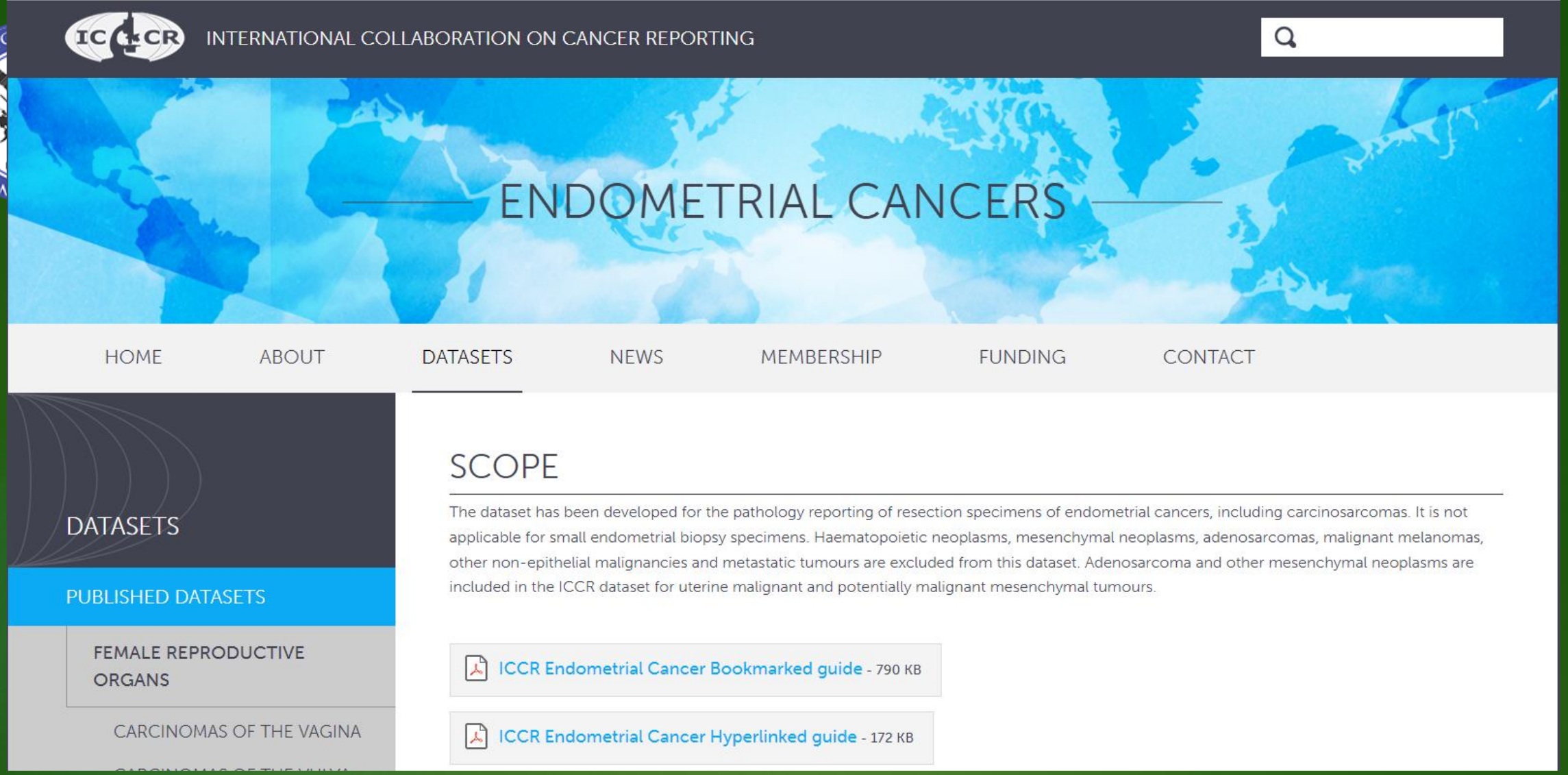
HKIAP 2023 Scientific Congress
Spring Scientific Meeting

UTERINE PATHOLOGY II: ENDOMETRIAL CANCER REPORTING BEYOND 2020 WHO CLASSIFICATION

PHILIP IP
CLINICAL PROFESSOR OF PATHOLOGY
SCHOOL OF CLINICAL MEDICINE
HKU

Learning Objectives: Endometrial Cancer Reporting beyond 2020 WHO Classification

- Standardize histopathology reporting for endometrial cancers.
- Aware of some tumors that are obviously high-grade but have an indolent behavior, and others that have a deceptively low-grade histology but are aggressive.
- Recognize the benefits of adopting a molecular classification for endometrial cancers.
- Acknowledge that there is life beyond the four TCGA molecular subgroups.



Matias-Guiu X, Anderson L, Buza N, Ellenson LH, Fadare O, Ganesan R, Ip PPC, Palacios J, Parra-Herran C, Raspollini MR, Soslow RA, Werner HMJ, Lax SF, McCluggage WG (2021). *Endometrial Cancer Histopathology Reporting Guide.* International Collaboration on Cancer Reporting; Sydney, Australia. ISBN: 978-1-922324-26-9.

http://www.iccr-cancer.org/datasets/published-datasets/female-reproductive/endometrial

Core elements (in BOLD) are those that are essential in a pathology report and must be stated.

HISTOLOGICAL TUMOUR TYPE (select all that apply) (Note 8)

(Value list based on the World Health Organization Classification of Female Genital Tumours (2020))

- ☐ Endometrioid carcinoma
- ☐ Serous carcinoma
- ☐ Clear cell carcinoma
- ☐ Carcinoma, undifferentiated
- ☐ Mixed cell carcinoma
- ☐ Mesonephric carcinoma
- ☐ Squamous cell carcinoma
- ☐ Mucinous carcinoma, gastrointestinal type
- ☐ Mesonephric-like carcinoma
- ☐ Neuroendocrine carcinomas
  - Specify subtype: _____
- ☐ Carcinosarcoma NOS → _____ % (Epithelial) AND _____ % (Sarcomatous)
  - ◯ Homologous
  - ◯ Heterologous
- ☐ Other, *specify*: _____

HISTOLOGICAL TUMOUR GRADE (Note 9)

- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Grade 1 (low)
- ◯ Grade 2 (low)
- ◯ Grade 3 (high)

MYOMETRIAL INVASION (Note 10)

◯ Not identified ◯ <50% ◯ ≥50%

Pattern of myometrial invasion, *specify*: _____

Absolute percentage of myometrial wall thickness invaded by carcinoma: _____ %

Distance of myoinvasive tumour to serosa: _____ mm

LYMPHOVASCULAR INVASION (Note 11)

- ◯ Indeterminate
- ◯ Not identified
- ◯ Present
  - **Extent of lymphovascular invasion**
    - ◯ Focal
    - ◯ Extensive/Substantial

CERVICAL STROMA (Note 14)

- ◯ Indeterminate
- ◯ Not involved
- ◯ Involved
  - **Depth of cervical stromal invasion** (Note 15): _____ mm
  - **Percentage of cervical stromal invasion**: _____ %

PARAMETRIA[a] (Note 16)

- ◯ Not involved
- ◯ Involved

VAGINA[a] (Note 17)

- ◯ Not involved
- ◯ Involved

OMENTUM[a] (Note 18)

- ◯ Not involved
- ◯ Involved

[a] *If submitted.*

Int J Gynecol Pathol. 2022;41(S1):S90-118

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- ☐ Neuroendocrine carcinomas
  - Specify subtype
- ☐ Carcinosarcoma NOS → % (Epithelial) AND % (Sarcomatous)
  - ◯ Homologous
  - ◯ Heterologous
- ☐ Other, *specify*

Endometrioid: squamous, mucinous, villoglandular, small nonvillous papillae, microglandular, sex cord-like, corded and hyalinized, sertoliform.

Absolute percentage of myometrial wall thickness invaded by carcinoma %

Distance of myoinvasive tumour to serosa mm

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- ◯ Indeterminate
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mm

%

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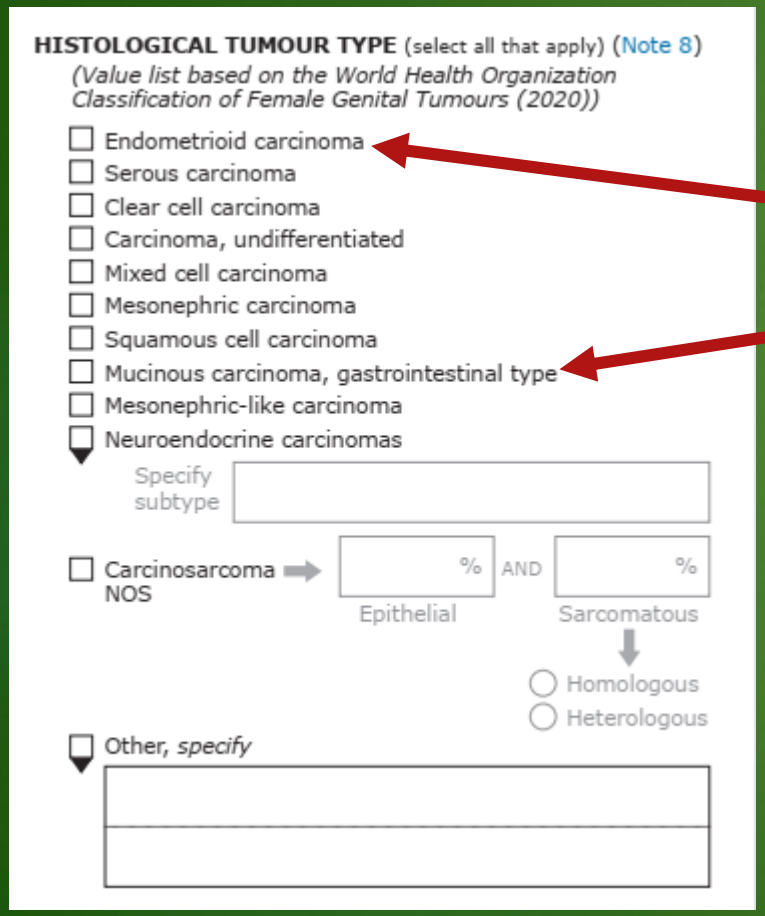
Endometrial mucinous carcinoma is assimilated into endometrioid carcinoma because of similar molecular features and natural history.

Mucinous carcinoma, gastrointestinal type.



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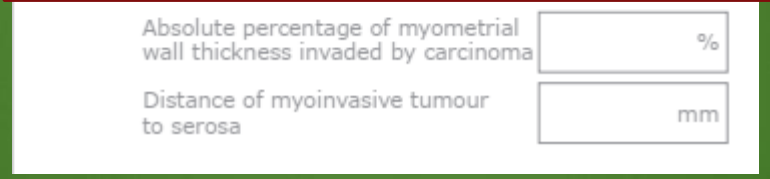
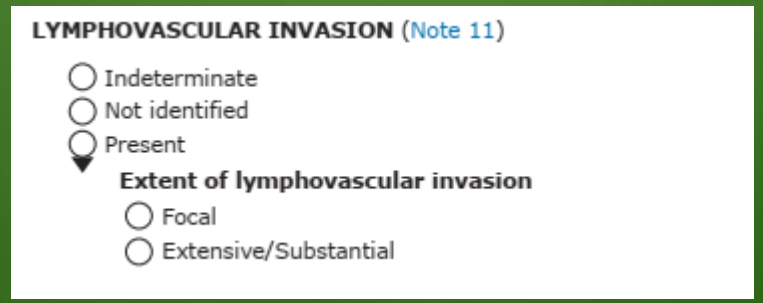


Absolute percentage of myometrial wall thickness invaded by carcinoma %

Distance of myoinvasive tumour to serosa mm



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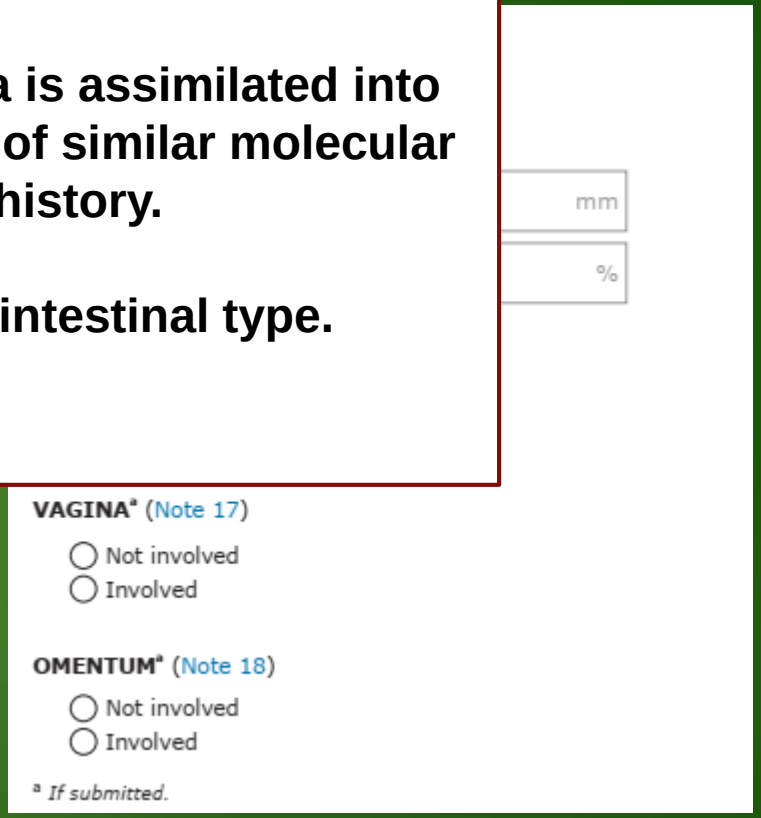

mm

%

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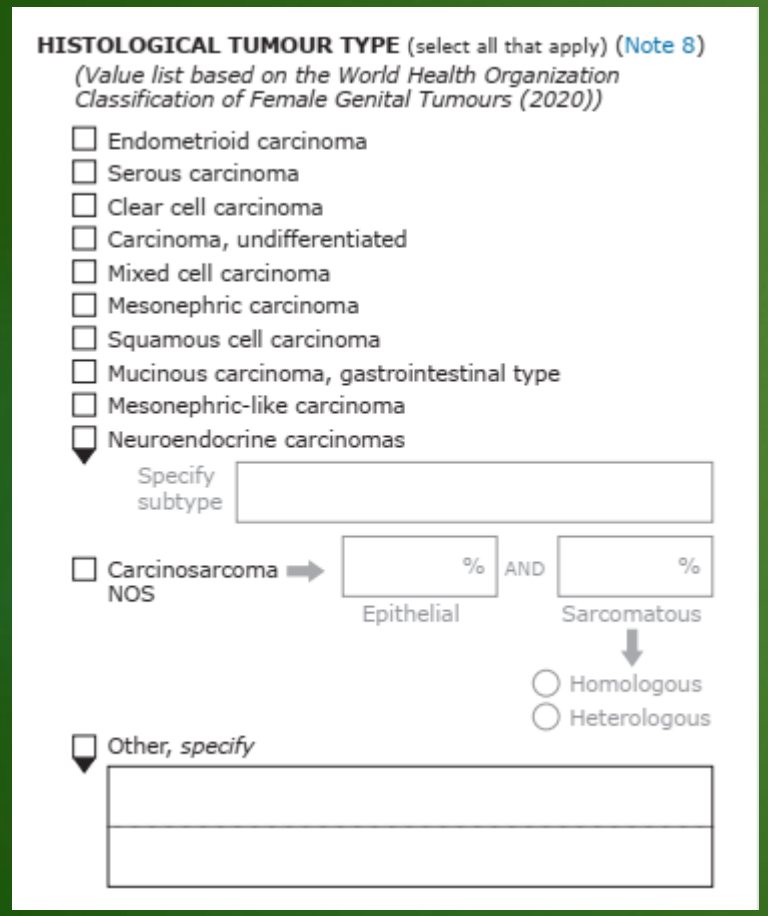

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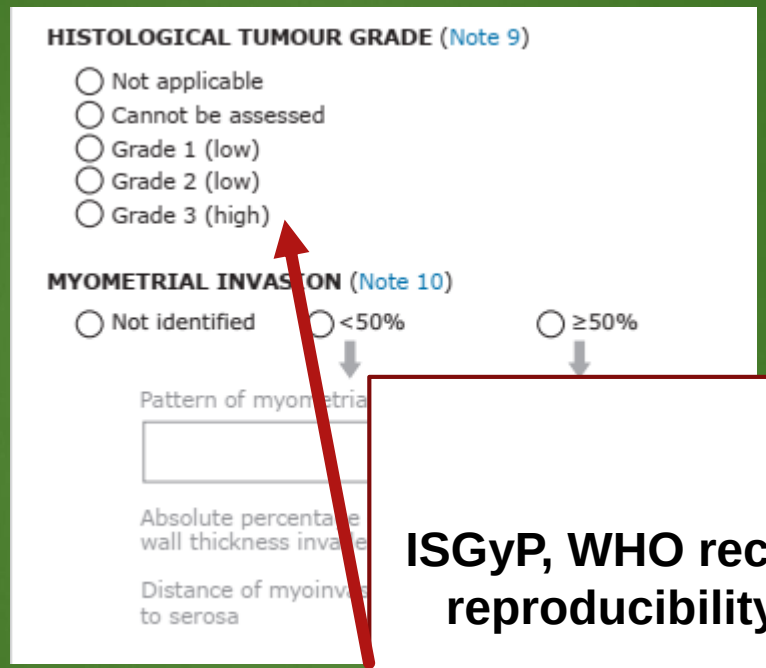

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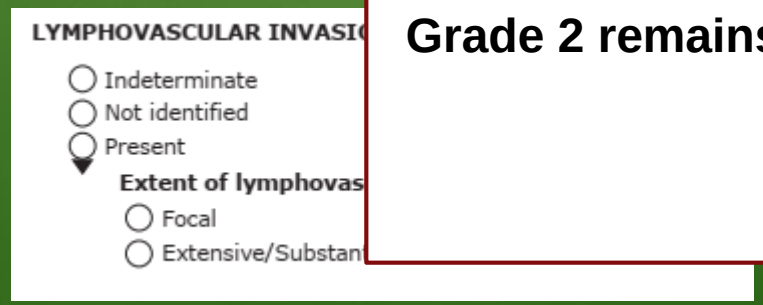
- ◯ ≥50%

Pattern of myometrial

Absolute percentage wall thickness invaded

Distance of myoinvasion to serosa



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  - **Extent of lymphovas**
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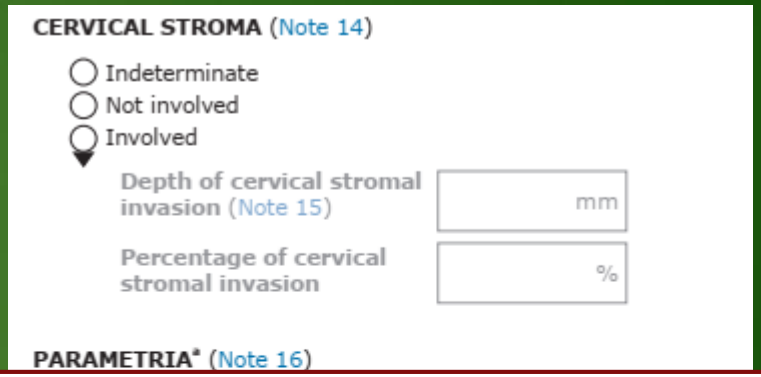

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  - Depth of cervical stromal invasion (Note 15) mm
  - Percentage of cervical stromal invasion %

PARAMETRIA[a] (Note 16)

ISGyP, WHO recommends binary grading for improved reproducibility and easier clinical decision making.

Grade 2 remains relevant for patients desiring fertility-sparing treatment.

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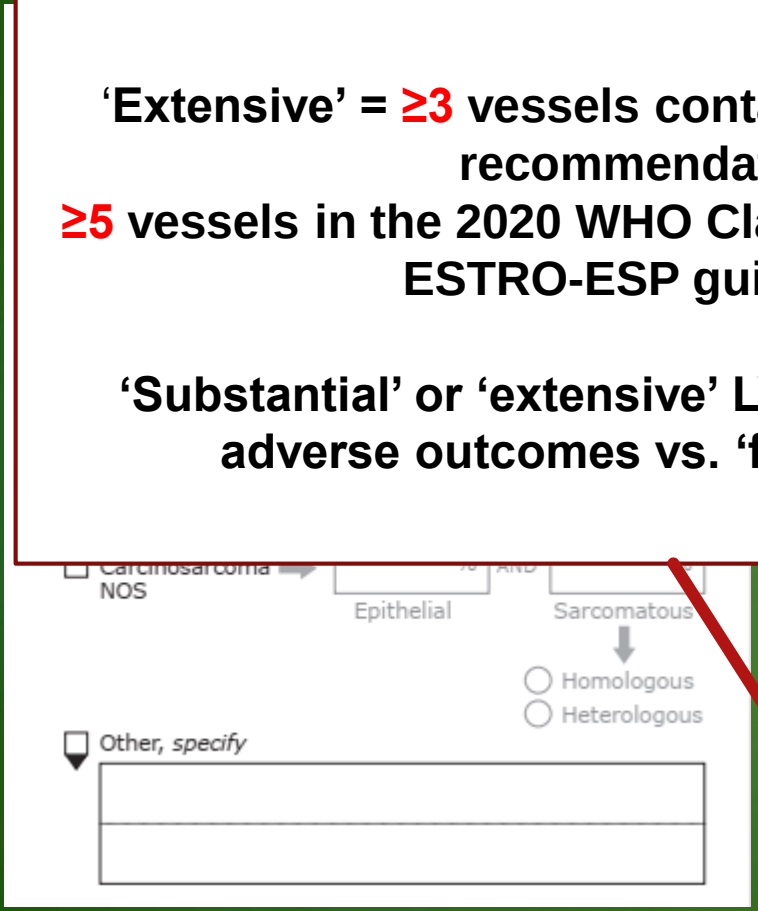
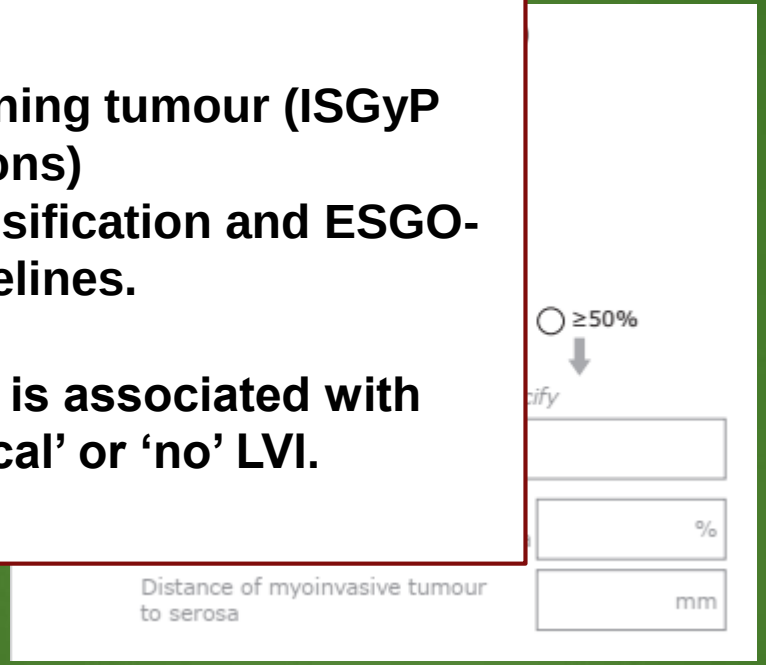
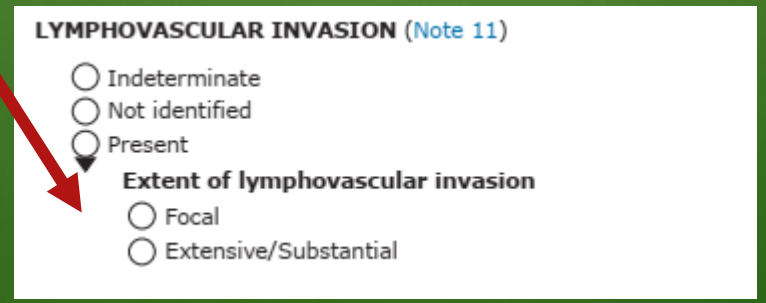
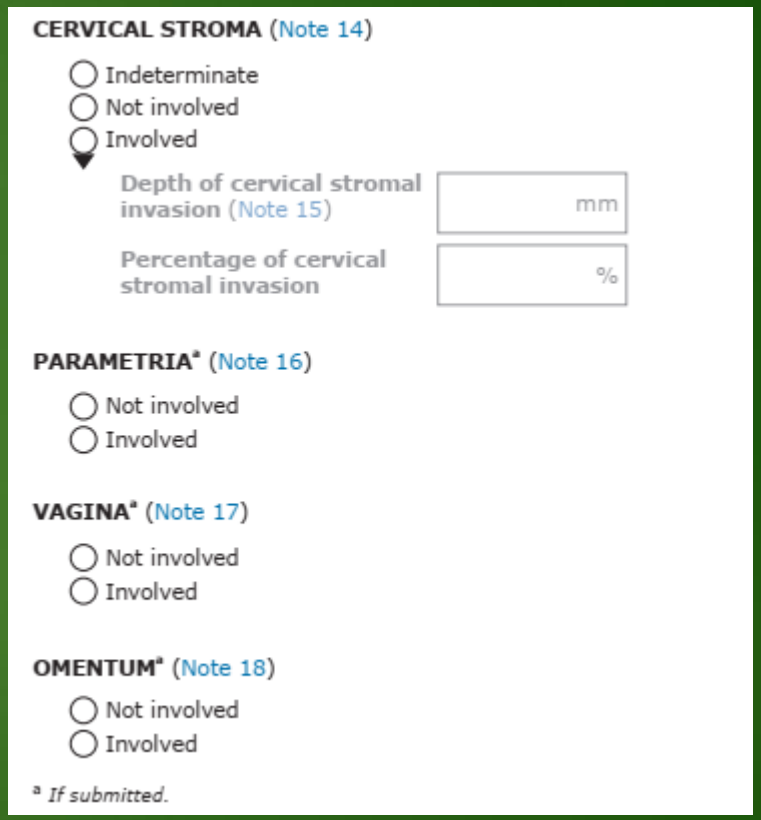
'Extensive' = ≥3 vessels containing tumour (ISGyP recommendations)
≥5 vessels in the 2020 WHO Classification and ESGO-ESTRO-ESP guidelines.

'Substantial' or 'extensive' LVI is associated with adverse outcomes vs. 'focal' or 'no' LVI.









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Ancillary studies for Molecular subtyping

ANCILLARY STUDIES (Note 26)

Performed (select all that apply) Not performed

- Mismatch repair testing, *specify*
- Immunohistochemistry, *specify test(s) and result(s)*
- Molecular findings, *specify test(s) and result(s)*
- TCGA-based molecular classification, *specify*
- Other, *specify test(s) and result(s)*

Representative blocks for ancillary studies, *specify those blocks best representing tumour and/or normal tissue for further study*

Testing for MMR status/microsatellite instability (MSI) in endometrial carcinoma patients has been shown to be important for four key reasons:

1. Diagnostic, since MMRd/MSI is helpful to diagnose endometrioid carcinomas (as opposed to serous carcinoma or human papillomavirus (HPV)-associated cervical carcinoma);
2. It is part of the screening algorithm to identify potential patients with Lynch syndrome;[228]
3. Prognostic, as part of the TCGA surrogate molecular classification;[229] and
4. Therapeutically as a predictive biomarker for potential utility of immune checkpoint inhibitor therapy.[230]

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ANCILLARY STUDIES (Note 26)

○ Performed (select all that apply) ☑ Not performed

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☐ TCGA-based molecular classification, *specify*

☐ Other, *specify test(s) and result(s)*

Representative blocks for ancillary studies, *specify those blocks best representing tumour and/or normal tissue for further study*

Table 1: World Health Organization classification of tumours of the uterine corpus.[3]

Descriptor	ICD-O codes[a]
Endometrial epithelial tumours and precursors	
Endometrial hyperplasia without atypia	
Atypical hyperplasia of the endometrium	8380/2
Endometrioid adenocarcinoma NOS	8380/3
POLE-ultramutated endometrioid carcinoma	
Mismatch repair-deficient endometrioid carcinoma	
P53-mutant endometrioid carcinoma	
No specific molecular profile (NSMP) endometrioid carcinoma	
Serous carcinoma NOS	8441/3
Clear cell adenocarcinoma NOS	8310/3
Carcinoma, undifferentiated, NOS	8020/3
Mixed cell adenocarcinoma	8323/3
Mesonephric adenocarcinoma	9110/3
Squamous cell carcinoma NOS	8070/3
Mucinous carcinoma, gastric (gastrointestinal)-type[b]	8144/3
Mesonephric-like adenocarcinoma	9113/3[c]
Carcinosarcoma NOS	8980/3
Neuroendocrine tumour NOS	8240/3

Treatment of Endometrial cancers

- Based on risk stratification (low, intermediate, and high) by using clinicopathological parameters (age, FIGO stage, **histologic type, grade**, lymphovascular space invasion, depth of invasion).

- Histotyping and grading, especially for higher grade carcinomas, suffer from poor interobserver reproducibility even among experienced gynecologic pathologists.

Murali R. et al. Int J Gynecol Pathol. 2019
Gilks CB. et al. Am J Surg Pathol. 2013
Han G. et al. Mod Pathol. 2013
Fadare O. et al. Am J Surg Pathol. 2012

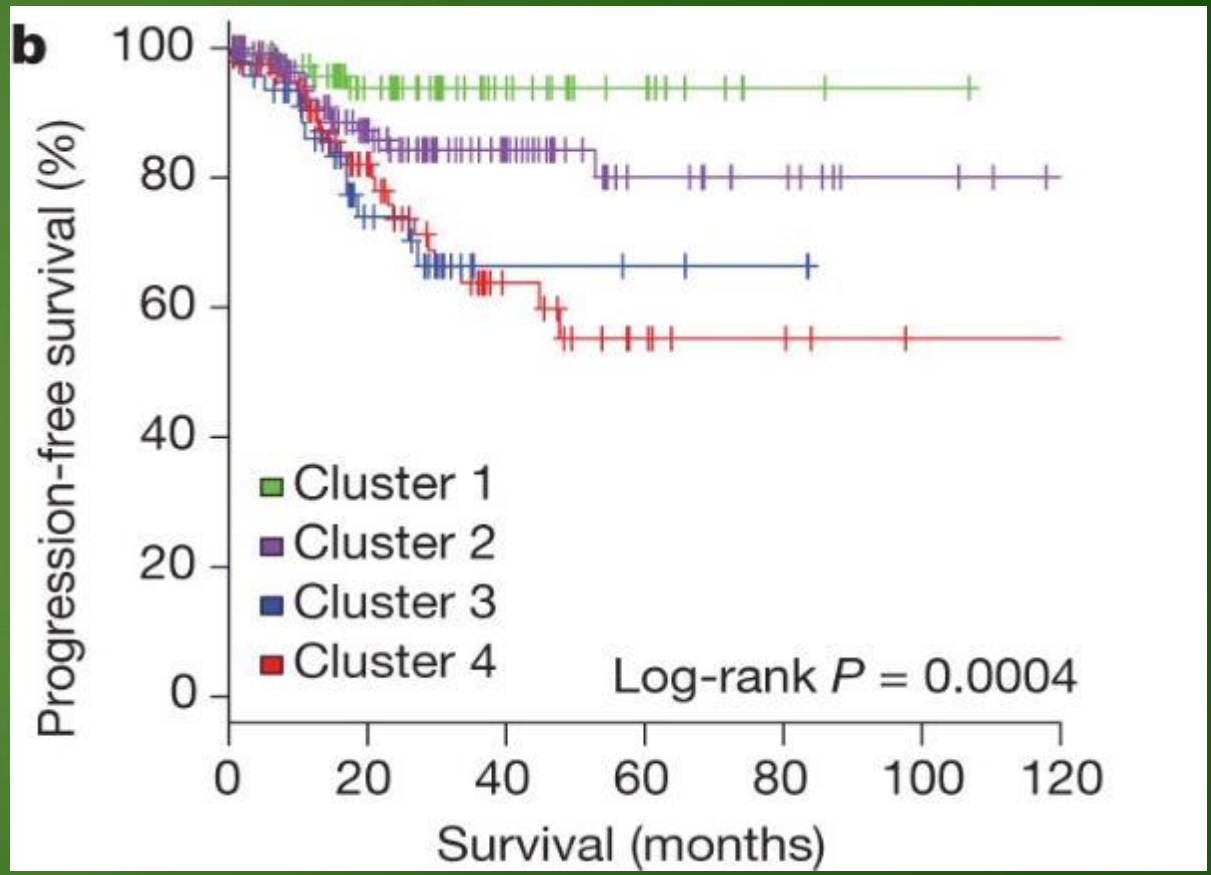
The Cancer Genome Atlas Project (TCGA): Molecular classification

1. *POLE* mutated endometrial carcinoma (ultramutated)

2. Mismatch Repair Deficient (MMR-d) endometrial carcinoma (hypermutated)

3. No Specific Molecular Profile endometrial carcinoma (NSMP, copy-number low)

4. p53abn endometrial carcinoma (serous-like, copy-number high)

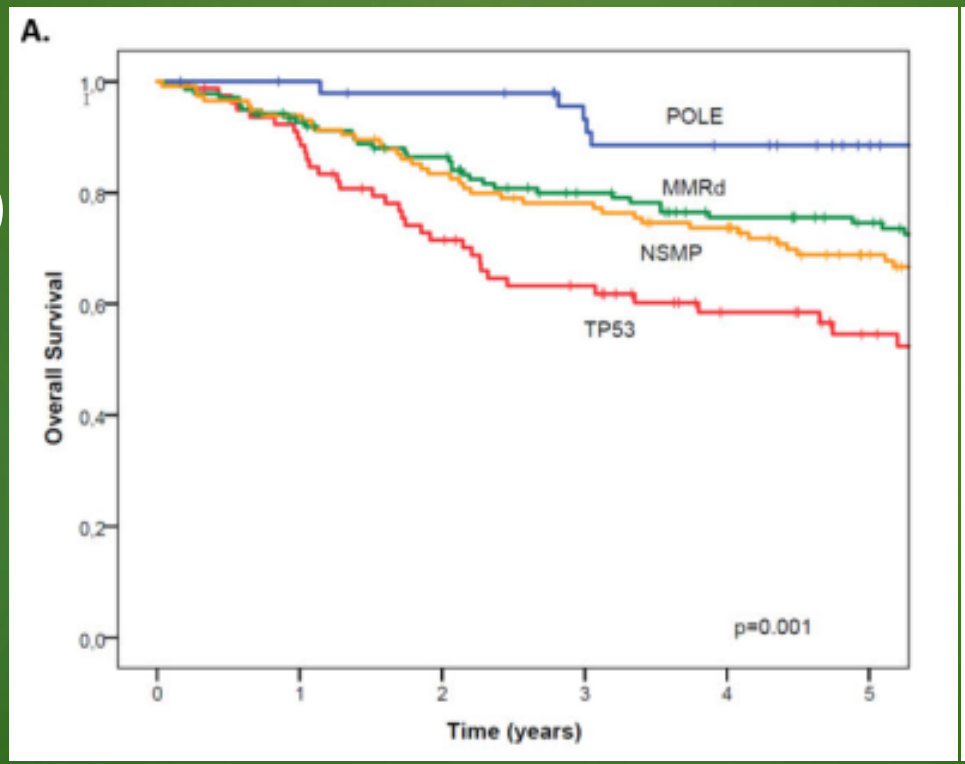


Kandoth C. Nature 2013

Molecular classification of grade 3 endometrioid endometrial cancers identifies distinct prognostic subgroups

Tjalling Bosse, MD[1], Remi A. Nout, MD[1], Jessica N. McAlpine, MD[2], Melissa K. McConechy, MD[3], Heidi Britton, MD[3], Yaser Hussein, MD[4], Carlene Gonzalez, BA[4], Raji Ganesan, MD[5], Jane C. Steele, MD[5], Beth T. Harrison, MD[6], Esther Oliva, MD[6], August Vidal, MD[7], Xavier Matias-Guiu, MD[7], Nadeem R. Abu-Rustum, MD[8], Douglas A. Levine, MD[8,*], C. Blake Gilks, MD[3], and Robert A. Soslow, MD[4]

- N=381
- POLE-mut 49 (12.9%)
- MMRd 138 (36.2%)
- NSMP 115 (30.2%)
- TP53-mut 79 (20.7%)



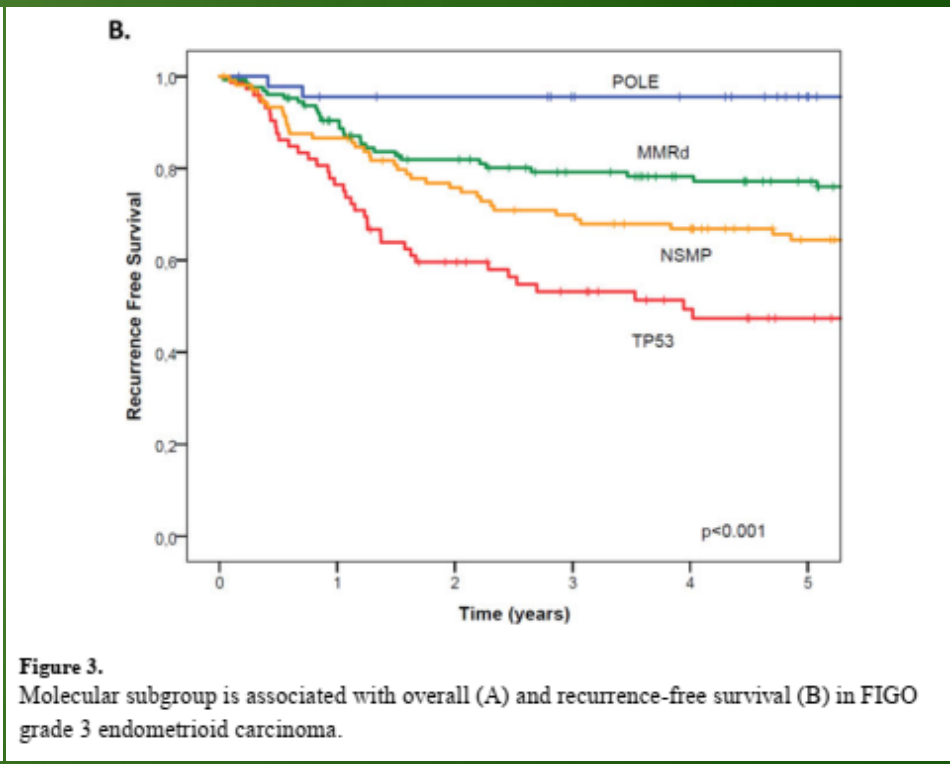


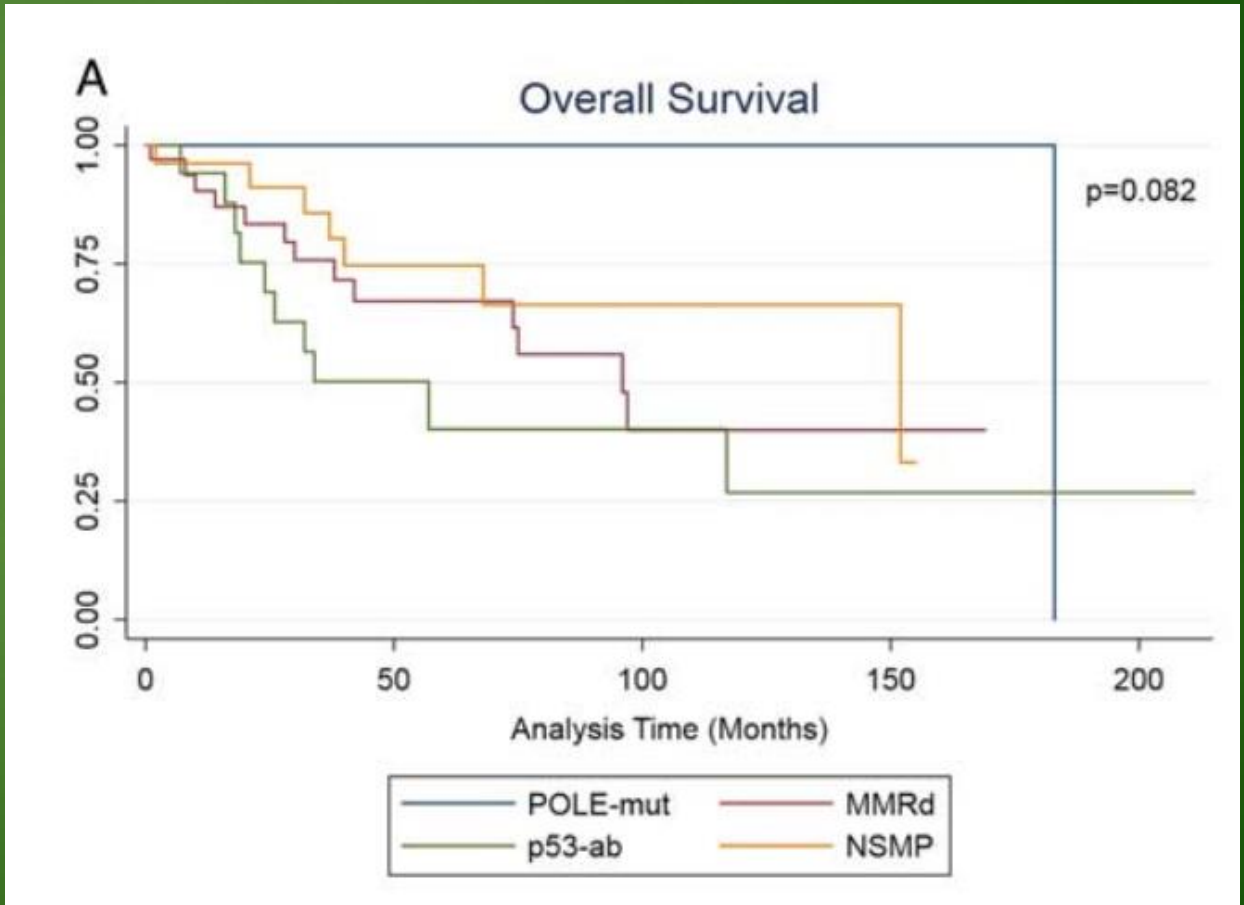
Figure 3.
Molecular subgroup is associated with overall (A) and recurrence-free survival (B) in FIGO grade 3 endometrioid carcinoma.

Bosse T. et al. Am J Surg Pathol. 2018

Molecularly Classified Uterine FIGO Grade 3 Endometrioid Carcinomas Show Distinctive Clinical Outcomes But Overlapping Morphologic Features

Amy Joehlin-Price, MD, Jessica Van Ziffle, PhD,† Nancy K. Hills, MA, PhD,‡ Nicholas Ladwig, MD,† Joseph T. Rabban, MD, MPH,† and Karuna Garg, MD†*

- N=95
- POLE-mut 10 (11%)
- MMRd 35 (37%)
- NSMP 26 (27%)
- TP53-mut 18 (19%)
- Multiple classifier 6 (6%)



Joehlin-Price A et al. Am J Surg Pathol. 2021

Molecular Classification of Endometrial Cancers

- Multiple independent retrospective and prospective studies have since demonstrated the reproducibility and prognostic significance of the four TCGA subgroups.

- WHO 2020 classification proposed the use of molecular classification into the diagnosis of endometrial cancers.

Talhouk A. et al. Cancer. 2017
Talhouk A. et al. Gynecol Oncol Res. Pract. 2016
Talhouk A. et al. Gynecol Oncol. 2016
Talhouk A. et al. Br J Cancer. 2015
Stelloo E. et al. Mod Pathol 2015

Molecular Classification of Endometrial Cancers

- Updated ICCR dataset for standardization of histopathology reporting.
- National Comprehensive Cancer Network (NCCN), and the joint European Society of Gynaecological Oncology (ESGO), European Society for Radiotherapy and Oncology (ESTRO), and European Society of Pathology (ESP) guidelines recommend **integration of molecular classification with clinicopathologic features**.
- Prospective trials using this integrative approach are underway for optimal cancer treatment management.

https://www.iccr-cancer.org/datasets/published-datasets/female-reproductive/endometrial/
https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf
https://doi.org/10.1007/s00428-020-03007-z

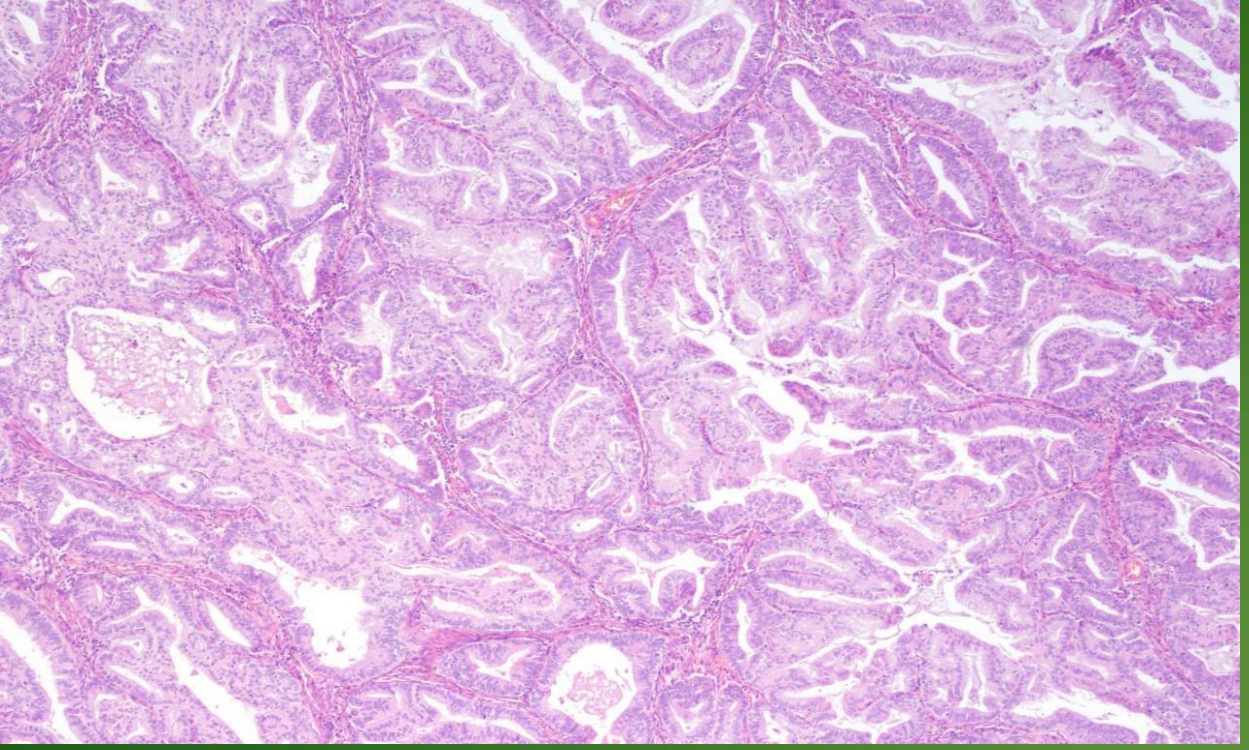
Integration of Molecular classification in Routine Diagnosis

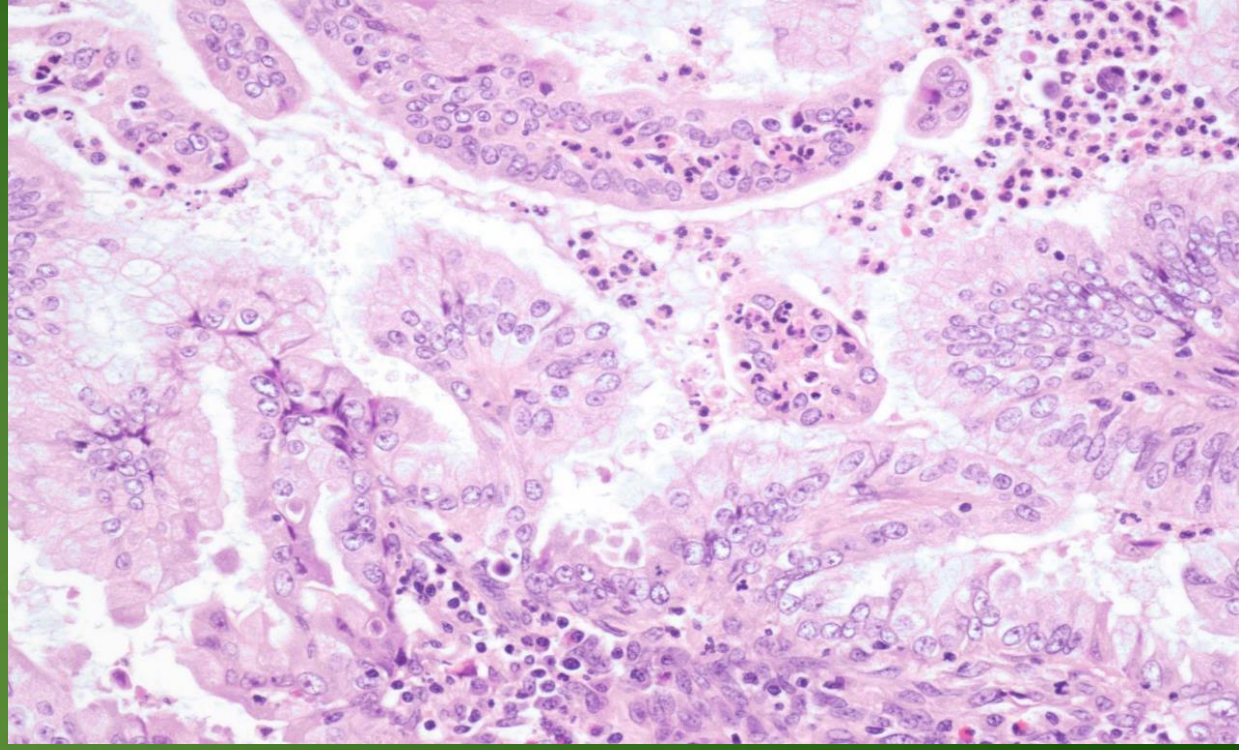
- Our current **action plans** should focus on optimize and implement the use of recommended surrogate markers in our routine signouts:

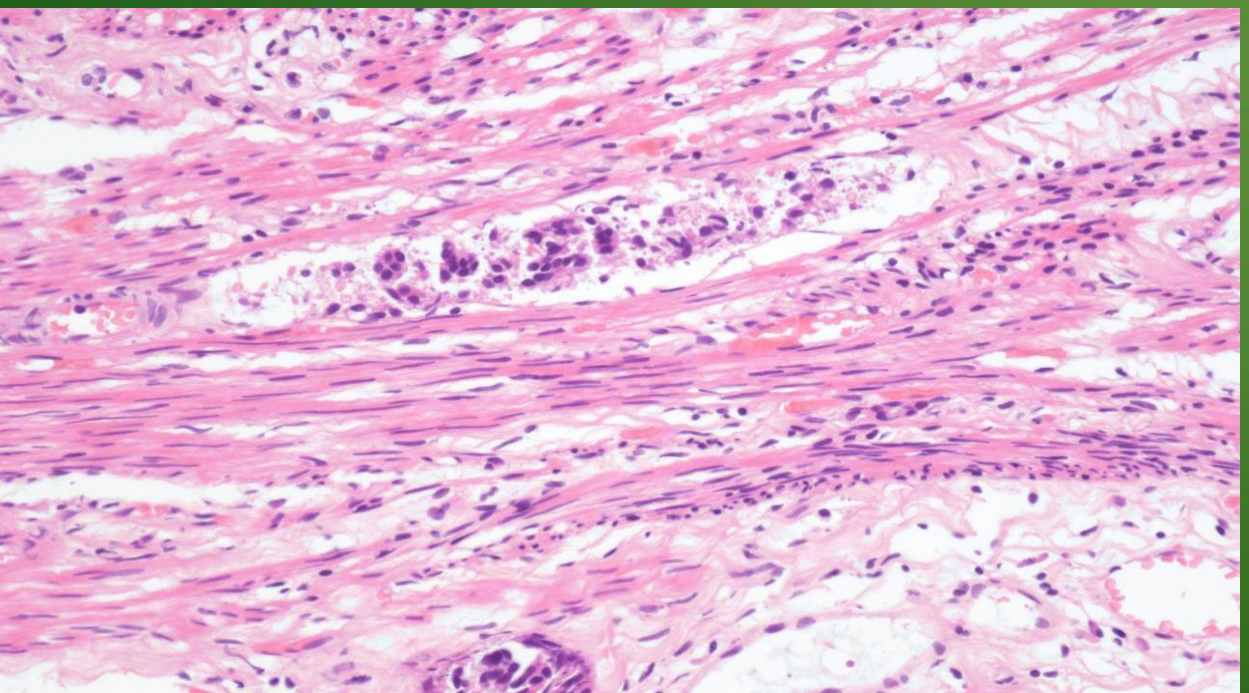
1. MMR immunohistochemistry (MLH1 promoter methylation, MSI)
2. p53 immunohistochemistry
3. *POLE* exonuclease domain hotspot mutations

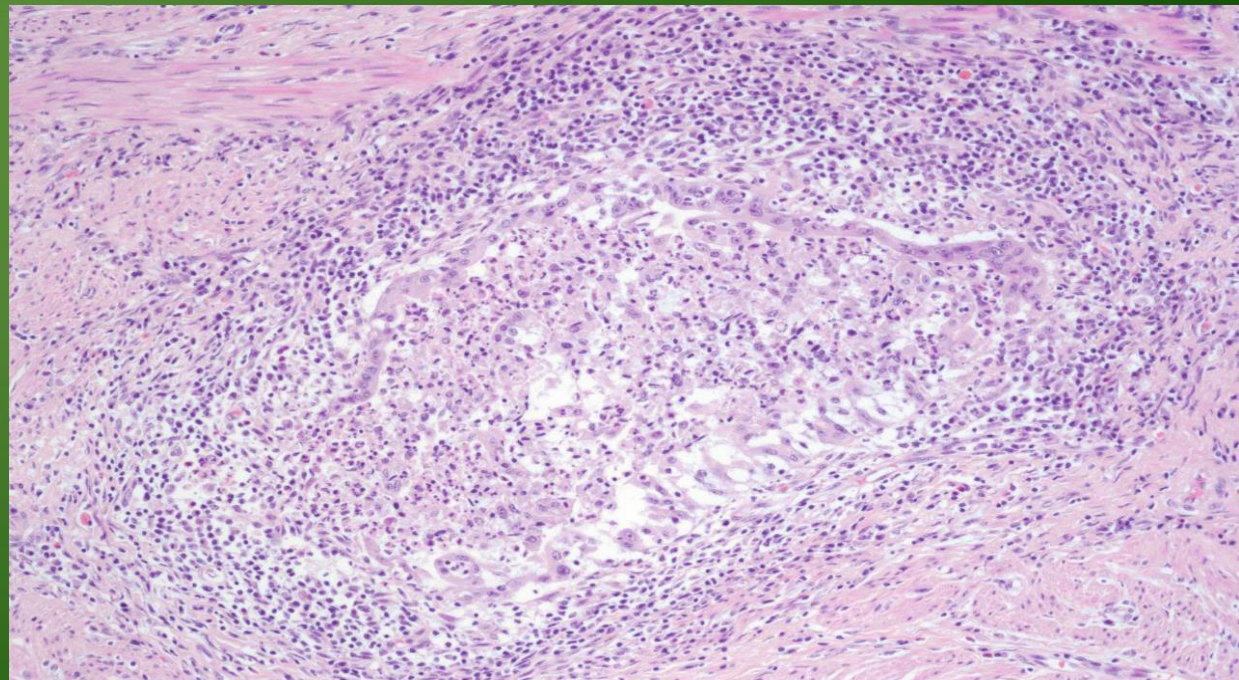
Adopting Molecular classification in Routine Diagnosis

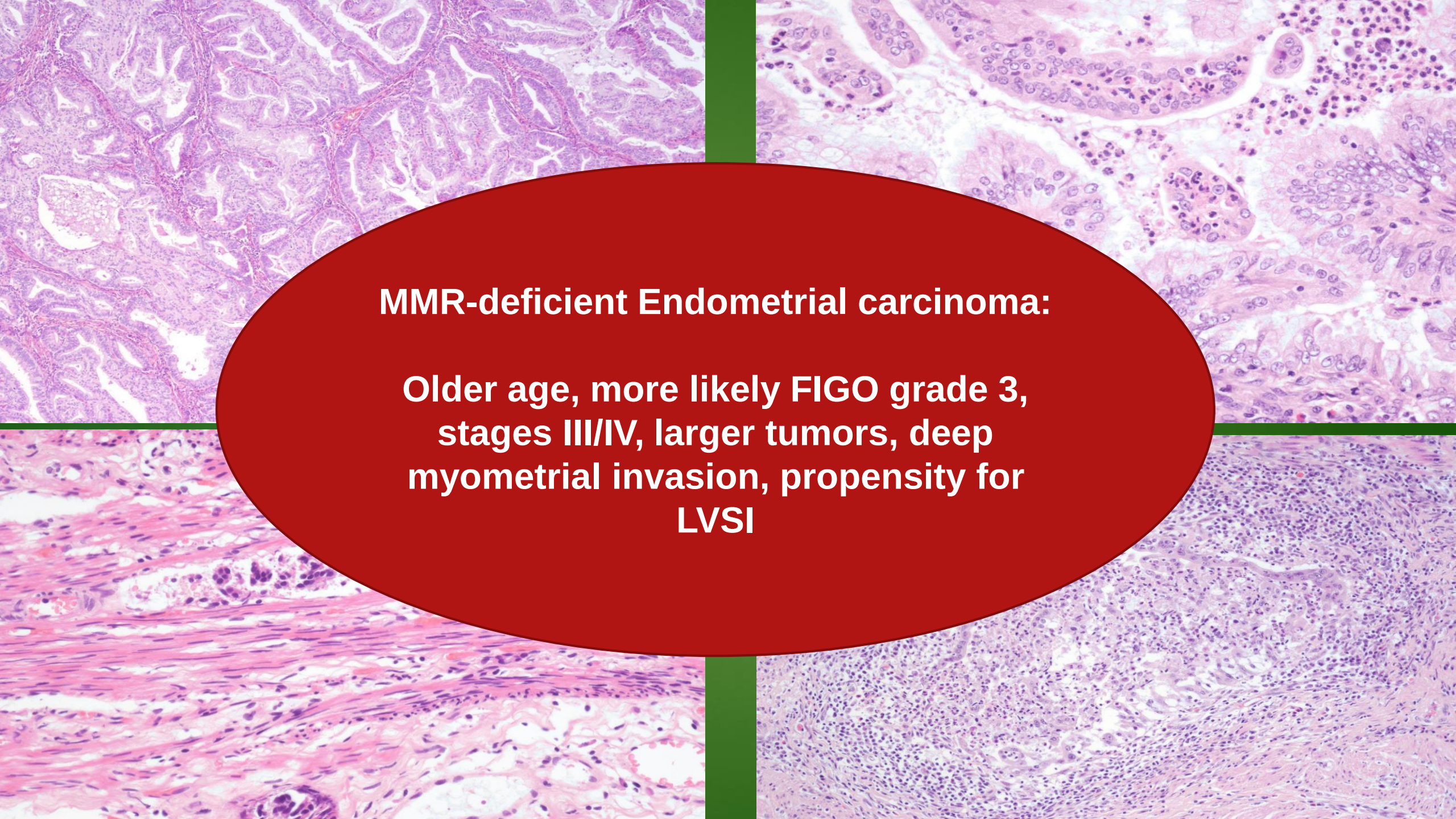
Rationale	Examples
Tumor typing	High grade carcinoma diagnosis. *TP53*-mutated low-grade endometrioid Ca into serous-like group. MMRd indicates endometrioid histology, endometrial > cervical. Subclonal IHC indicates tumor from a different subgroup.
Optimal management	De-escalation or withholding adjuvant treatment in stage I/II POLE mutants (improve quality of life). Immunotherapy for advanced stage or recurrent for MMRd cancers.
Hereditary Cancer Screening	Lynch syndrome (important for patient and her family).
Prognosis prediction	Life expectancy and make treatment decisions.







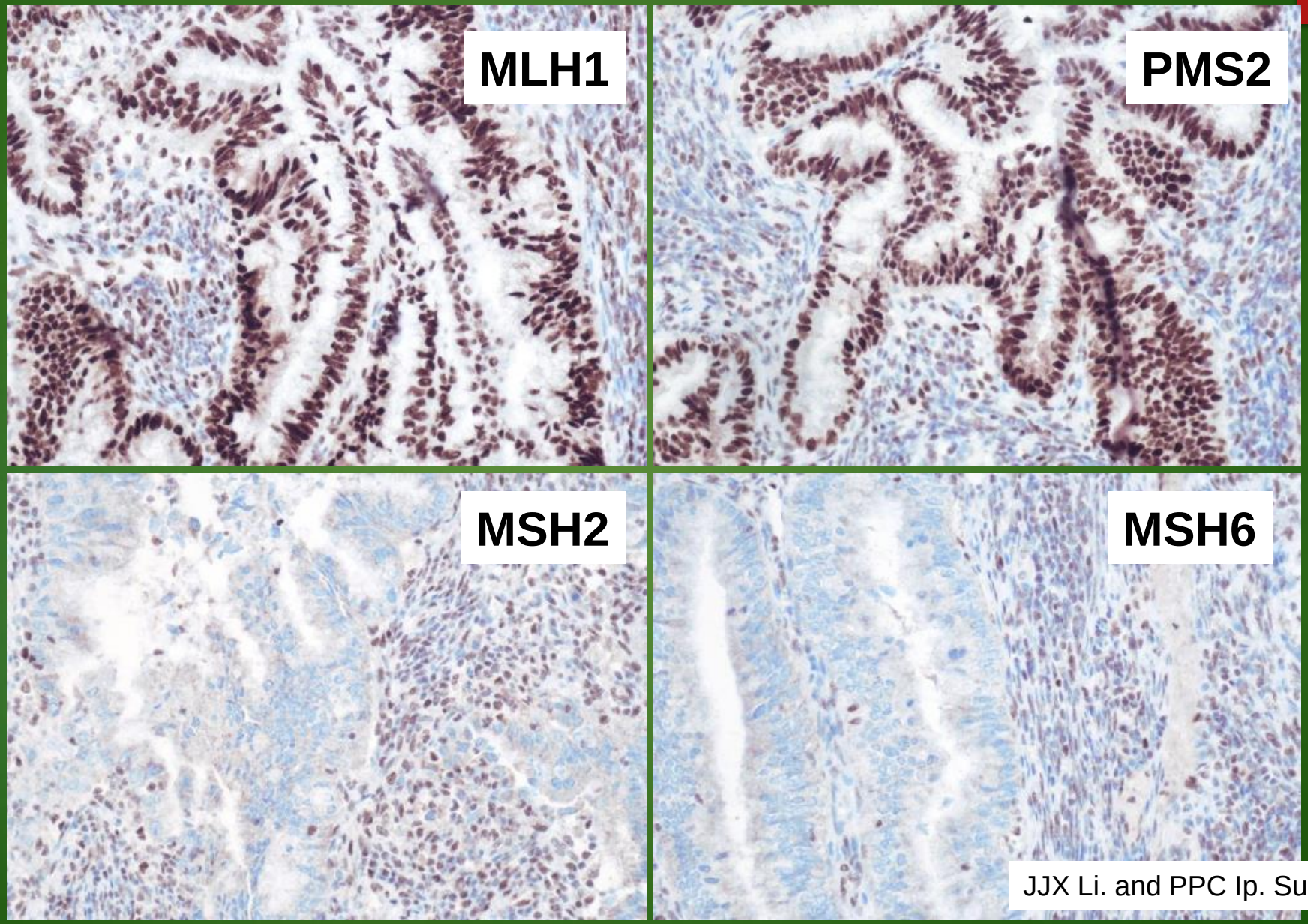




MMR-deficient Endometrial carcinoma:

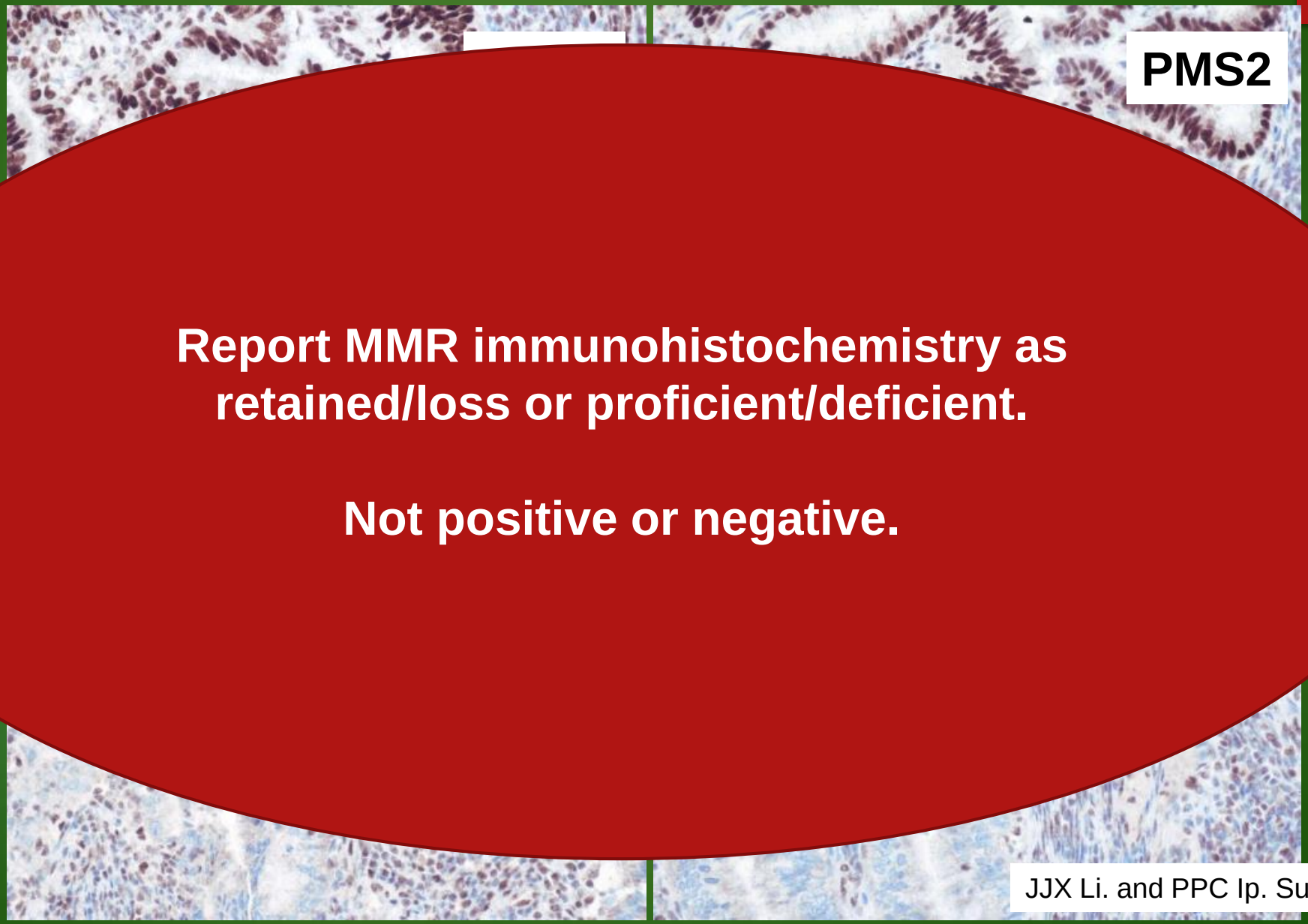
Older age, more likely FIGO grade 3, stages III/IV, larger tumors, deep myometrial invasion, propensity for LVSI

Reporting MMR immunohistochemistry



JJX Li. and PPC Ip. Surg Pathol Clin. 2022

Reporting MMR immunohistochemistry



Report MMR immunohistochemistry as retained/loss or proficient/deficient.

Not positive or negative.

JJX Li. and PPC Ip. Surg Pathol Clin. 2022

Clinicopathological significance of deficient DNA mismatch repair and *MLH1* promoter methylation in endometrioid endometrial carcinoma

Annukka Pasanen[1,2] · Mikko Loukovaara[3] · Ralf Bützow[1,2,3]

- **MMR Proficient 438 (64.2%)**
- **MMR Deficient 244 (35.8%)**
  - MLH1 + PMS2 loss (29.8%) with 91% due to MLH1 promoter methylation
  - Isolated PMS2 loss (0.9%)
  - MSH2 + MSH6 loss (1.3%)
  - Isolated MSH6 loss (2.8%)
  - MLH1 + PMS2 + MSH6 loss (1%)

Pasanen A. et al. Mod Pathol. 2020
Watkins JC. et al. Int J Gynecol Pathol. 2017
Goodfellow PJ. et al. J Clin Oncol. 2015
Bruegl AS. et al. Curr Pharm Des. 2014

MMRp vs MMRd Endometrial Cancers

	MMR proficient *n* (%)	MMR deficient *n* (%)	*P* value
N, total	438	244	
Age at diagnosis (mean ± SD)	65.9 ± 10.3	69.5 ± 9.8	**<0.001**
Grade 1–2	385/438 (87.9)	190/244 (77.9)	**0.001**
Grade 3	53/438 (12.2)	54/244 (22.1)	
Stage I	364/438 (83.1)	184/244 (75.4)	**0.015**
Stage II–IV	74/438 (16.9)	60/244 (19.6)	
Myometrial invasion ≥50%	147/438 (33.6)	99/244 (40.6)	0.068
Lymphovascular invasion	88/429 (20.5)	63/244 (25.8)	0.113
Peritoneal cytology +	22/431 (5.1)	7/240 (2.9)	0.182
Tumor size ≥2 cm	297/408 (72.8)	183/227 (80.6)	**0.028**
Abundant TILs	74/419 (17.7)	73/235 (31.3)	**<0.001**
PD-L1 tumor cells ≥1%	32/419 (7.6)	22/235 (9.4)	0.442
PD-L1 immune cells ≥1%	76/419 (20.4)	97/235 (41.3)	**<0.001**
PD-L1 CPS ≥1%	50/419 (11.9)	62/235 (26.4)	**<0.001**
ER <10%	36/426 (8.5)	24/235 (10.2)	0.450
PR <10%	78/431 (18.1)	47/233 (20.2)	0.514

- MMRd group: those with MLH1 promoter methylation were >70y, tumors ≥2 cm (p<0.001).

Pasanen A. et al. Mod Pathol 2020

MLH1-methylated Endometrial Cancers

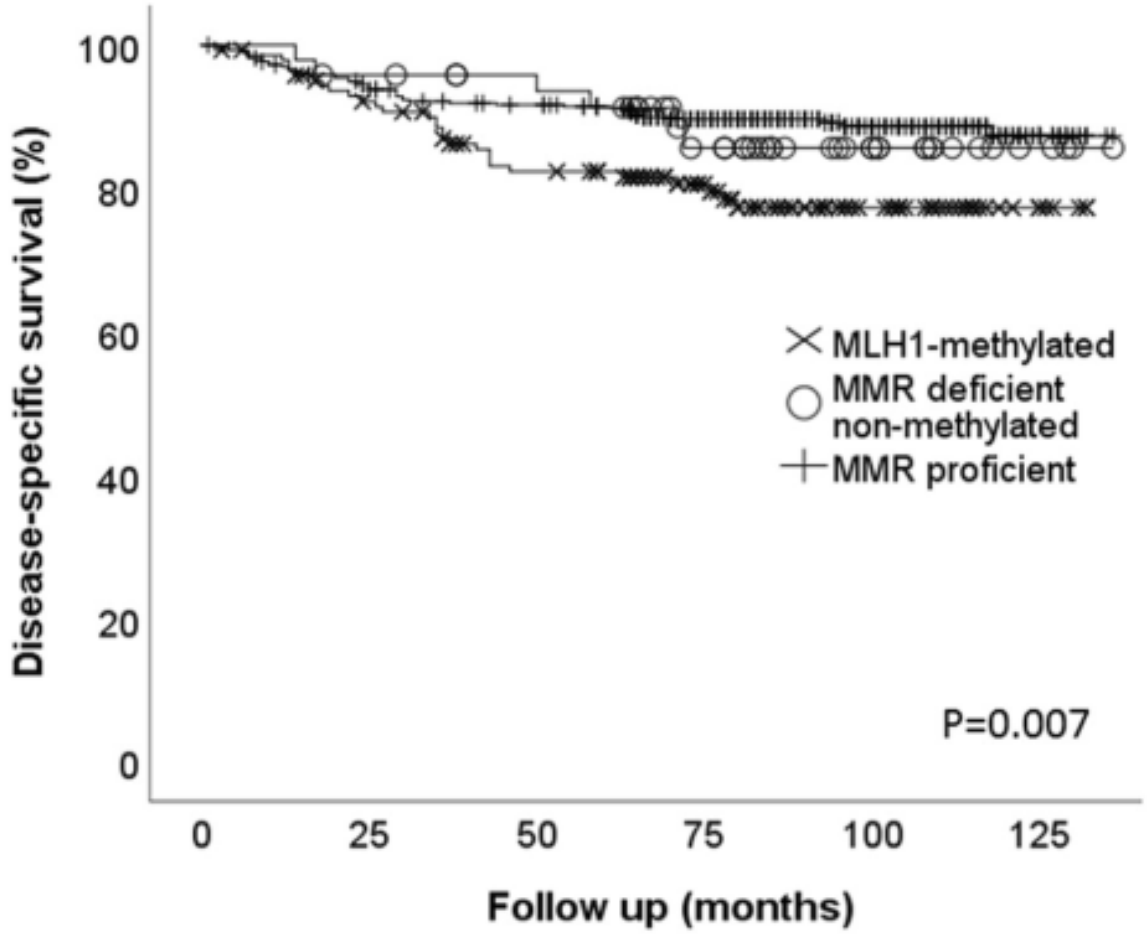
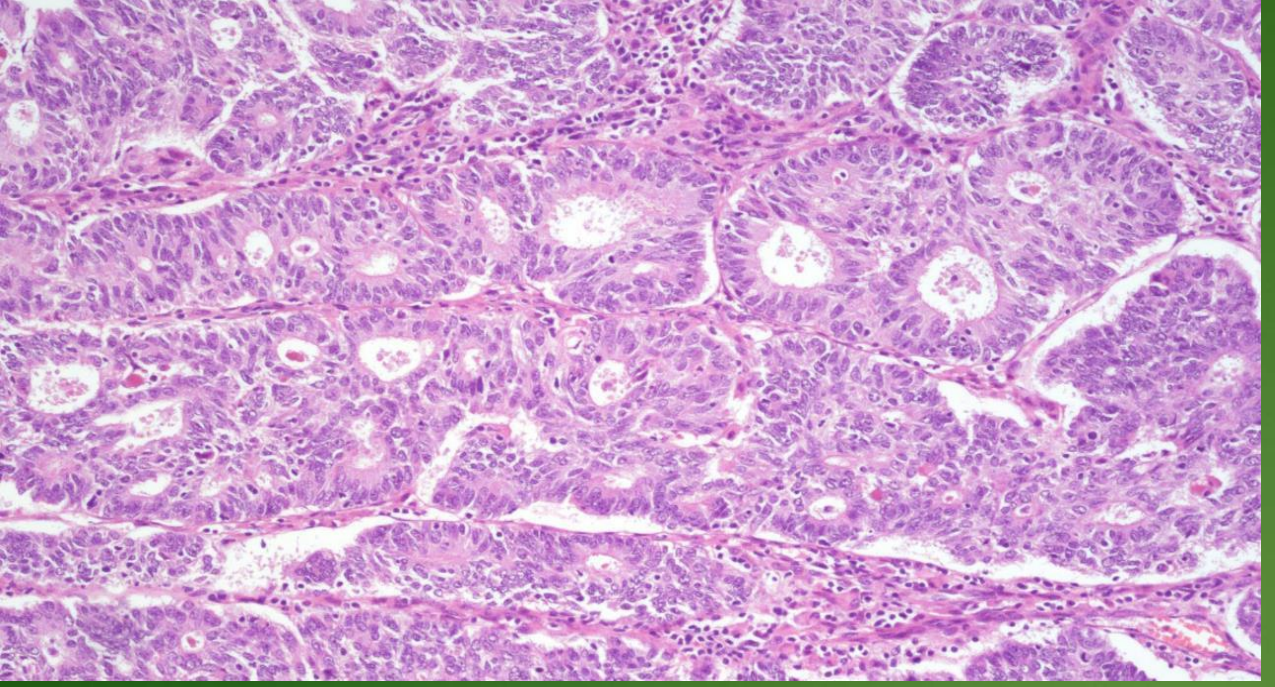
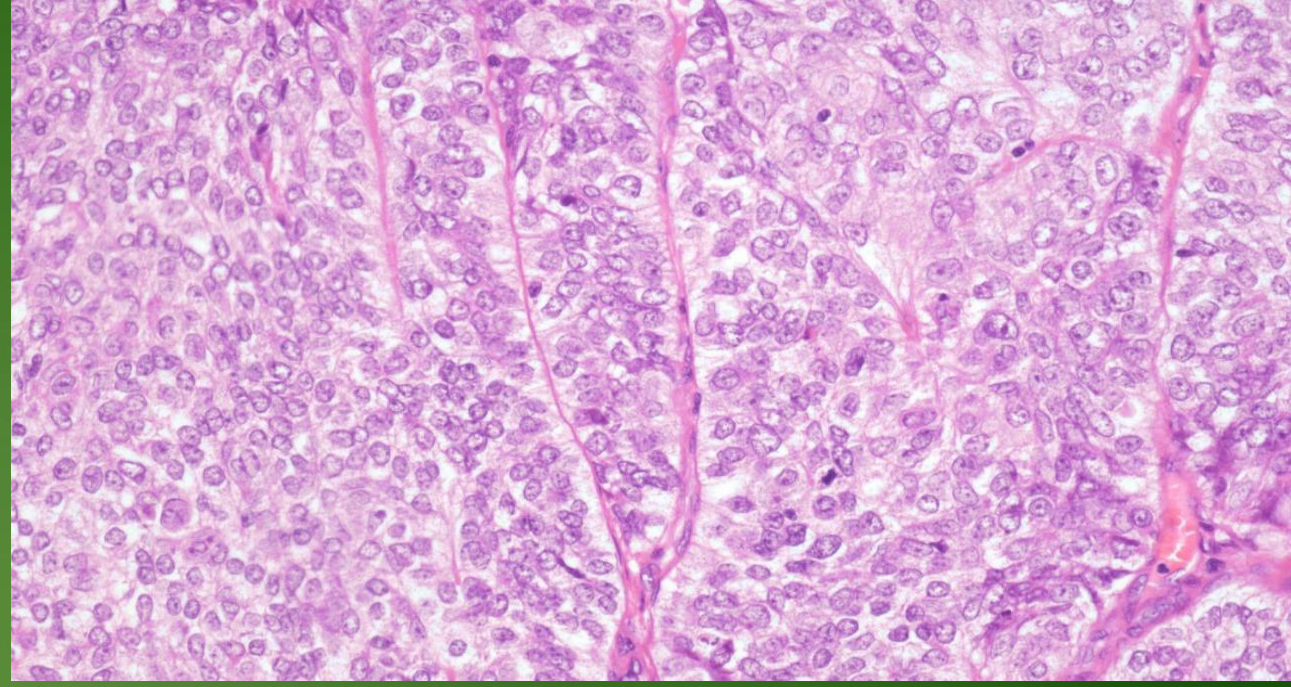
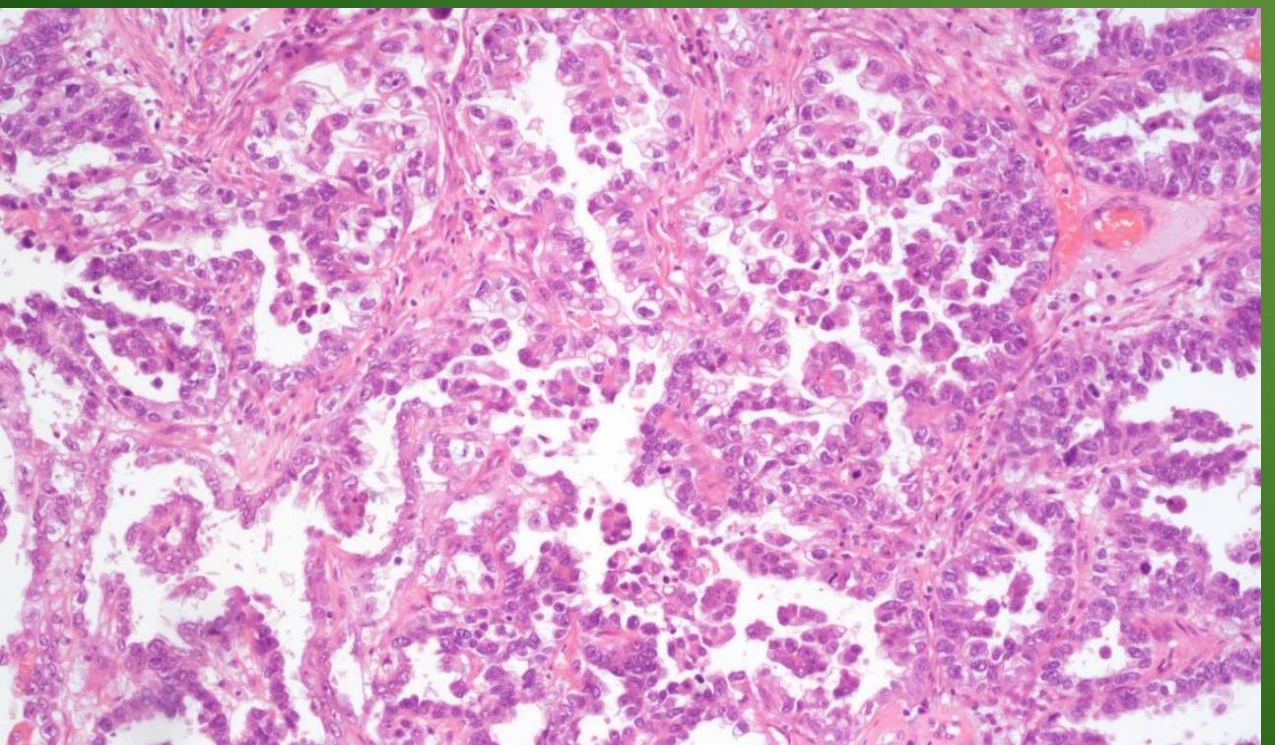
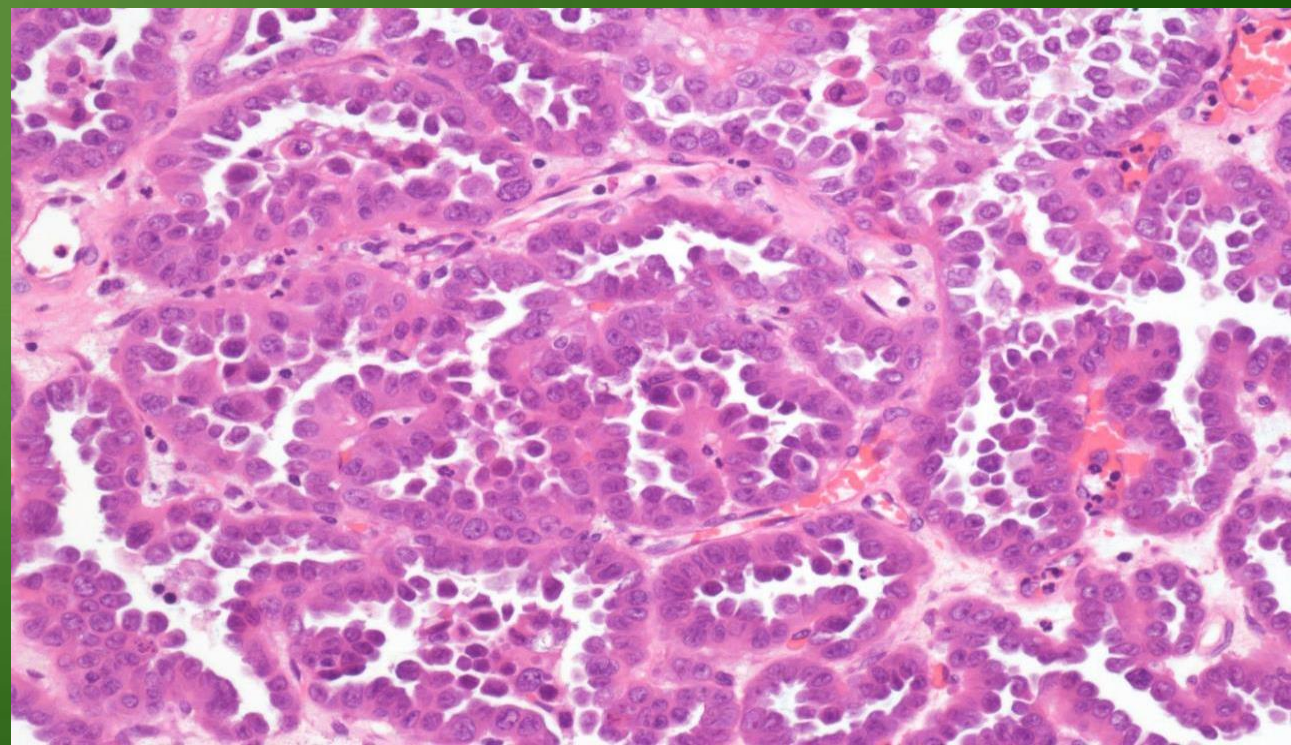


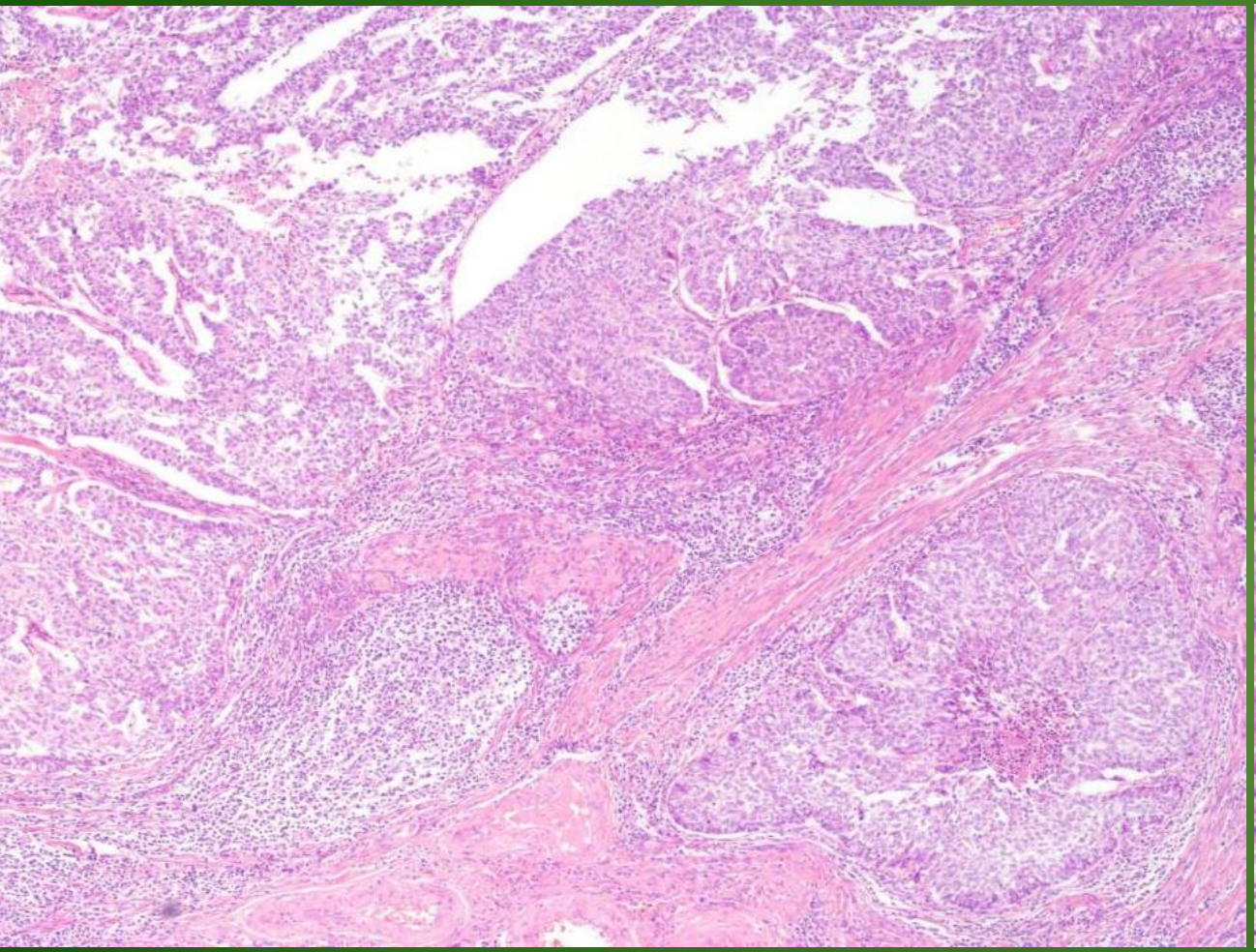
Fig. 3 Disease-specific survival according to the MMR phenotype.

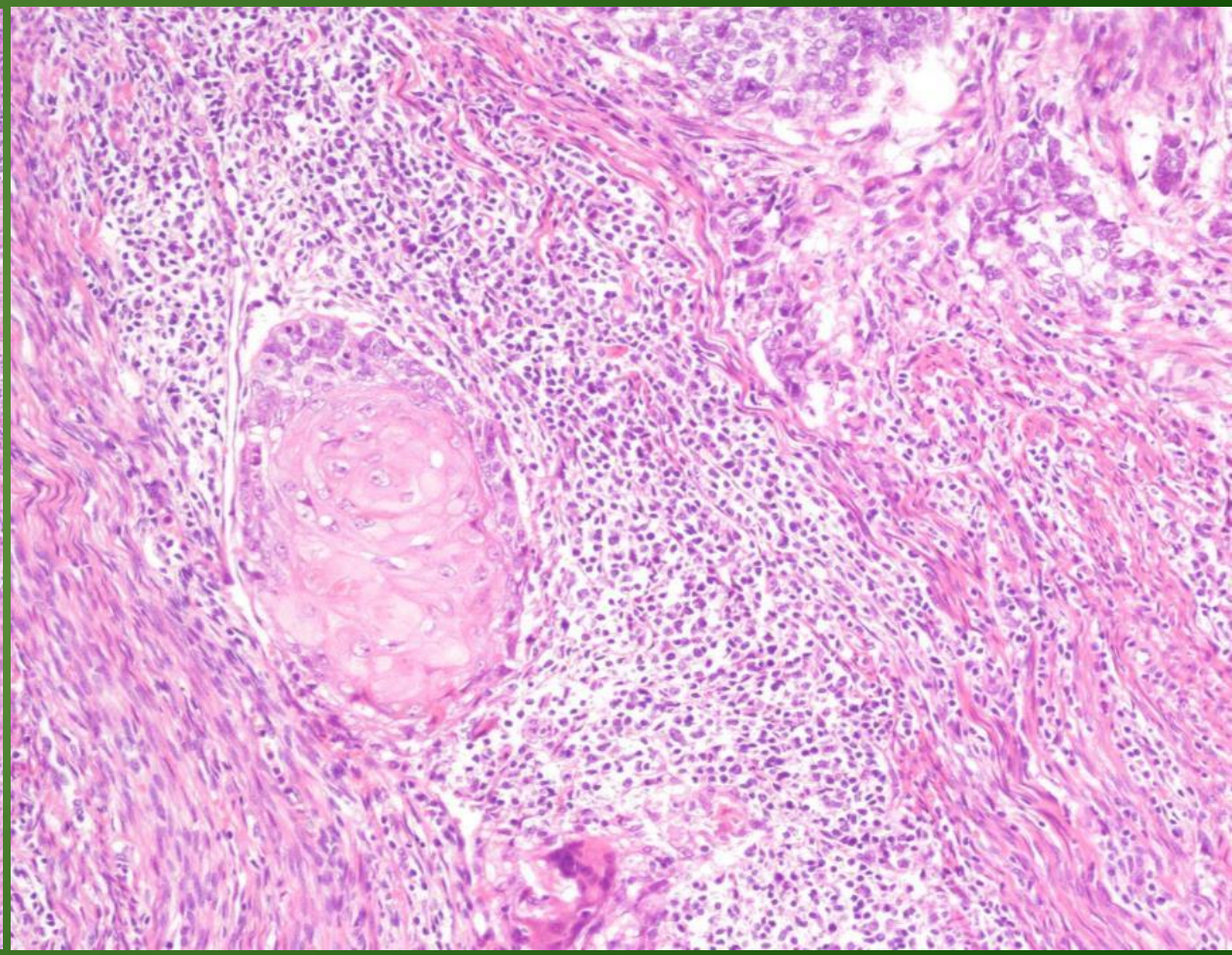
	DFS	OS	
MMR methylated	83.2%	71.3%	*P*=0.007
MMR-non methylated	91.7%	83.3%	

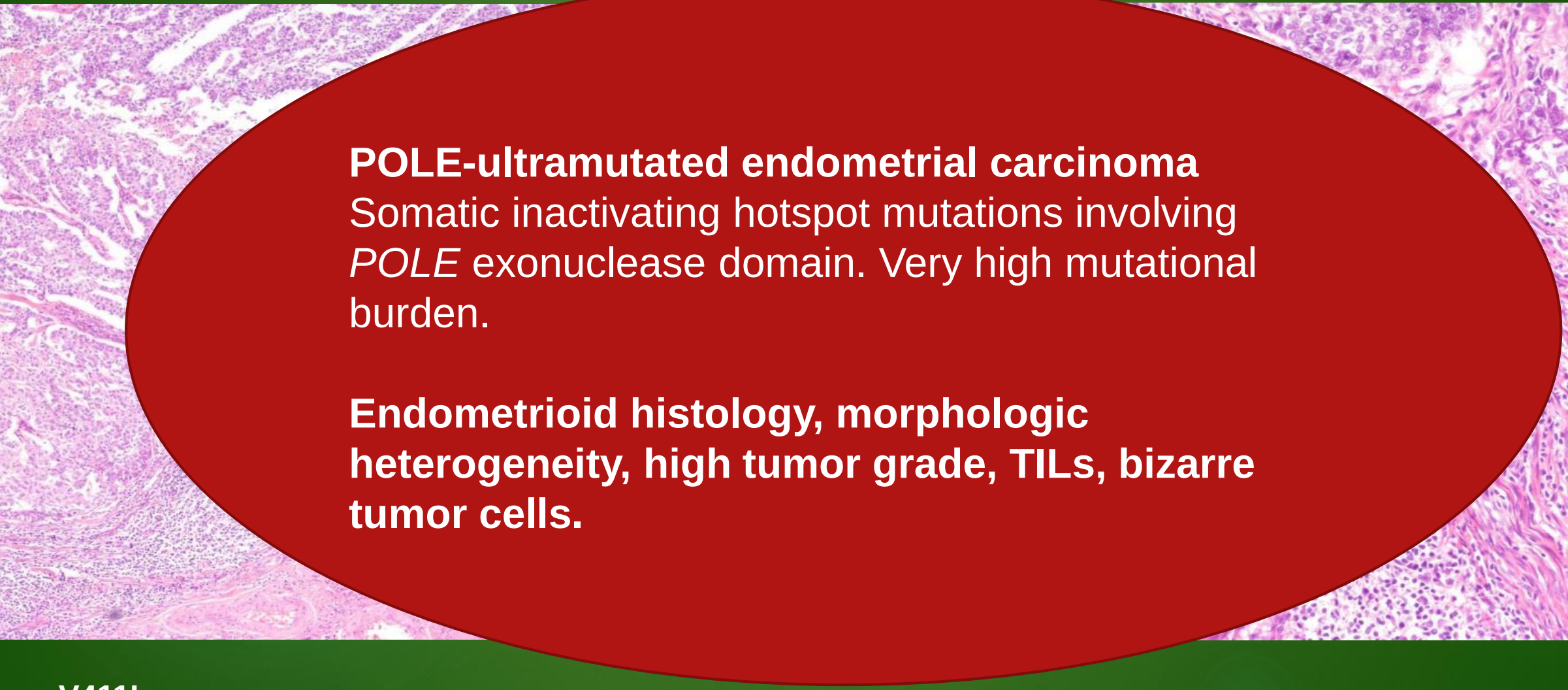
- MMRd-Met phenotype predicted lower disease-specific survival.

Pasanen A. et al. Mod Pathol 2020
Cosgrove DM. et al. Gynecol Oncol. 2017







POLE-ultramutated endometrial carcinoma
Somatic inactivating hotspot mutations involving *POLE* exonuclease domain. Very high mutational burden.

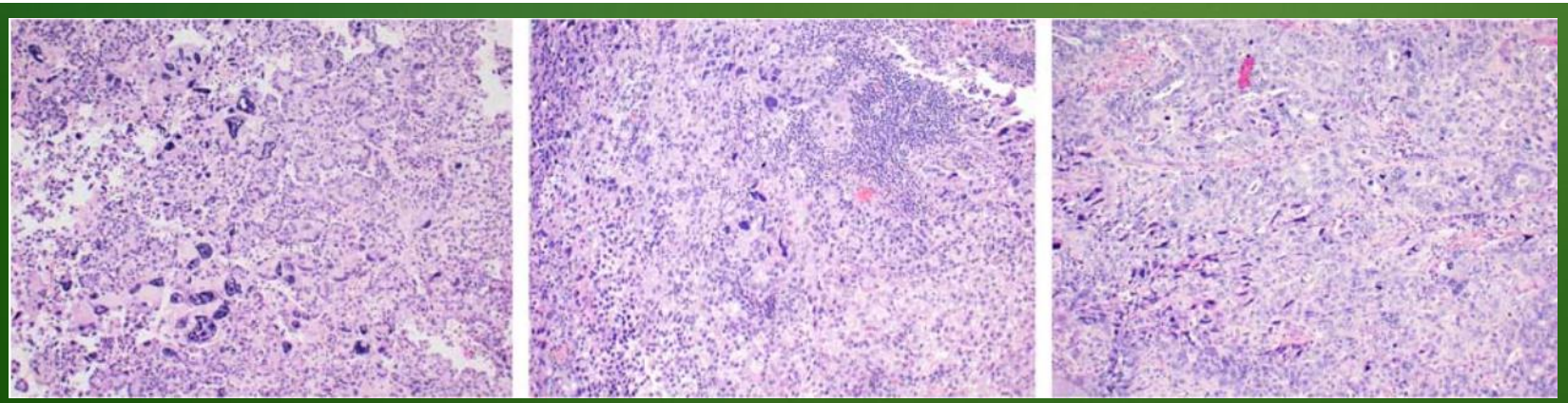
Endometrioid histology, morphologic heterogeneity, high tumor grade, TILs, bizarre tumor cells.

V411L

Molecularly Classified Uterine FIGO Grade 3 Endometrioid Carcinomas Show Distinctive Clinical Outcomes But Overlapping Morphologic Features

Amy Joehlin-Price, MD, Jessica Van Ziffle, PhD,† Nancy K. Hills, MA, PhD,‡ Nicholas Ladwig, MD,† Joseph T. Rabban, MD, MPH,† and Karuna Garg, MD†*

	POLE-mut (N=10)	MMR-d (N=35)	p53-ab (N=18)	NSMP (N=26)	MultClass (N=6)	Total Cases (N=95)	*P*
Morphologic characteristics							
Low-grade EEC component	6 (60)	30 (86)	12 (67)	19 (73)	5 (83)	72 (76)	0.22
Squamous differentiation	6 (60)	25 (71)	10 (56)	17 (65)	4 (67)	62 (65)	0.69
Mucinous differentiation	2 (20)	15 (43)	2 (11)	4 (15)	0 (0)	23 (24)	0.03
Necrosis	6 (60)	20 (57)	12 (67)	12 (46)	4 (67)	54 (57)	0.60
Bizarre atypia	9 (90)	7 (20)	13 (72)	7 (27)	6 (100)	42 (44)	<0.001
Tumor heterogeneity	3 (30)	20 (57)	6 (33)	4 (15)	6 (100)	39 (41)	0.008
Peritumoral lymphocytes	10 (100)	24 (68)	12 (67)	9 (35)	5 (83)	60 (63)	0.001
TILs	8 (80)	26 (74)	9 (50)	12 (46)	5 (83)	60 (63)	0.06
Any LVI	3 (30)	19 (54)	13 (72)	12 (46)	2 (33)	49 (52)	0.16
Extensive LVI	1 (10)	9 (26)	6 (33)	5 (19)	0 (0)	21 (22)	0.55



Joehlin-Price A et al. Am J Surg Pathol. 2021

POLE-ultramutated endometrial carcinoma

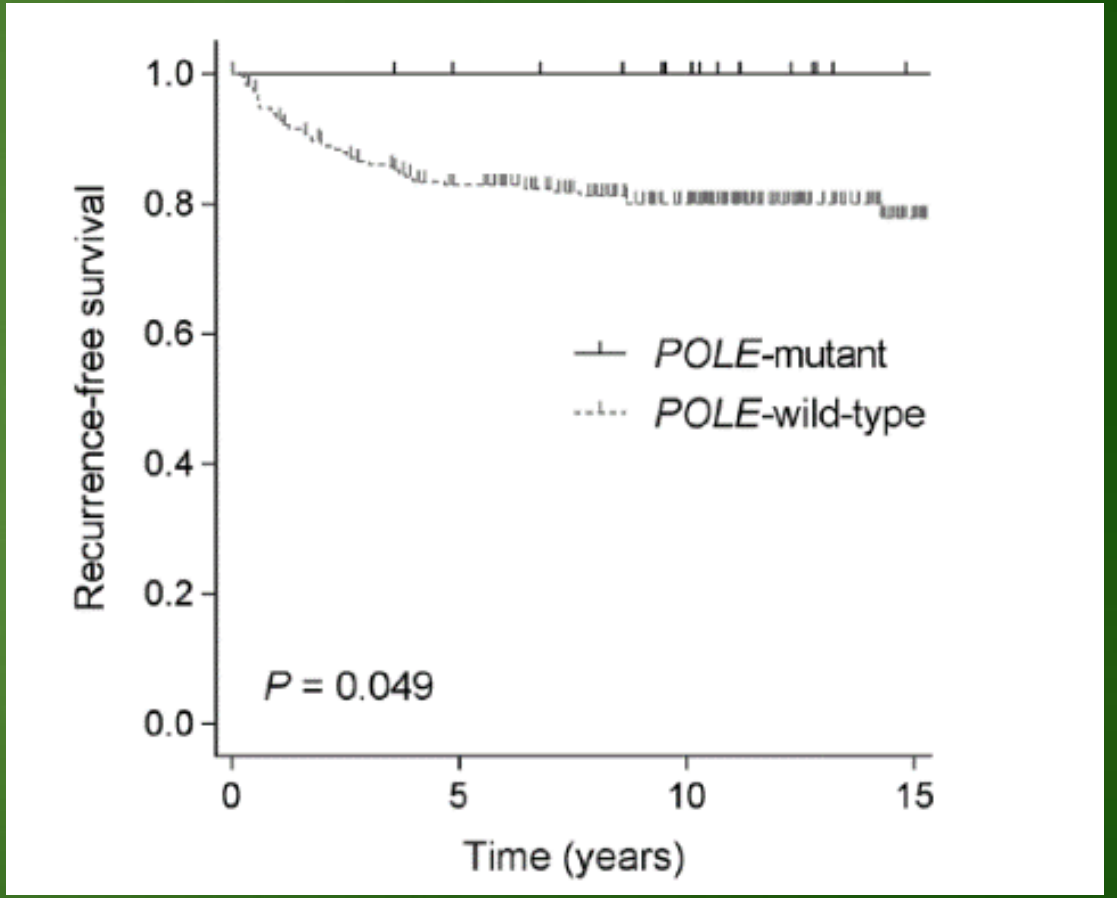
- Currently, tumors with high-grade features are categorized in higher clinical risk groups, and ultimately received adjuvant therapy.

- Many studies and trials results have highlighted the clinical importance of recognising *POLE* ultramutated endometrial carcinoma.

Leon-Castillo A. et al. J Patho. 2020
Leon-Castillo A. et al. J Clin Oncol. 2020
Vermij L. et al. Histopathology. 2020
Stasenko M. Gynecol Oncol. 2020
McAlpine J. et al. Cancer. 2021
Kommoss S. Ann Oncol. 2018
Billingsley CC. Int J Gynecol Cancer. 2016
Church DN. J Natl Cancer Inst. 2015

POLE-ultramutated endometrial carcinoma

- Prospective PORTEC-1 trial observational arm (no adjuvant therapy). Patients with *POLE* mutated cancers have better survival.
- Likely due to high mutational burden that led to augmented host immunity response.

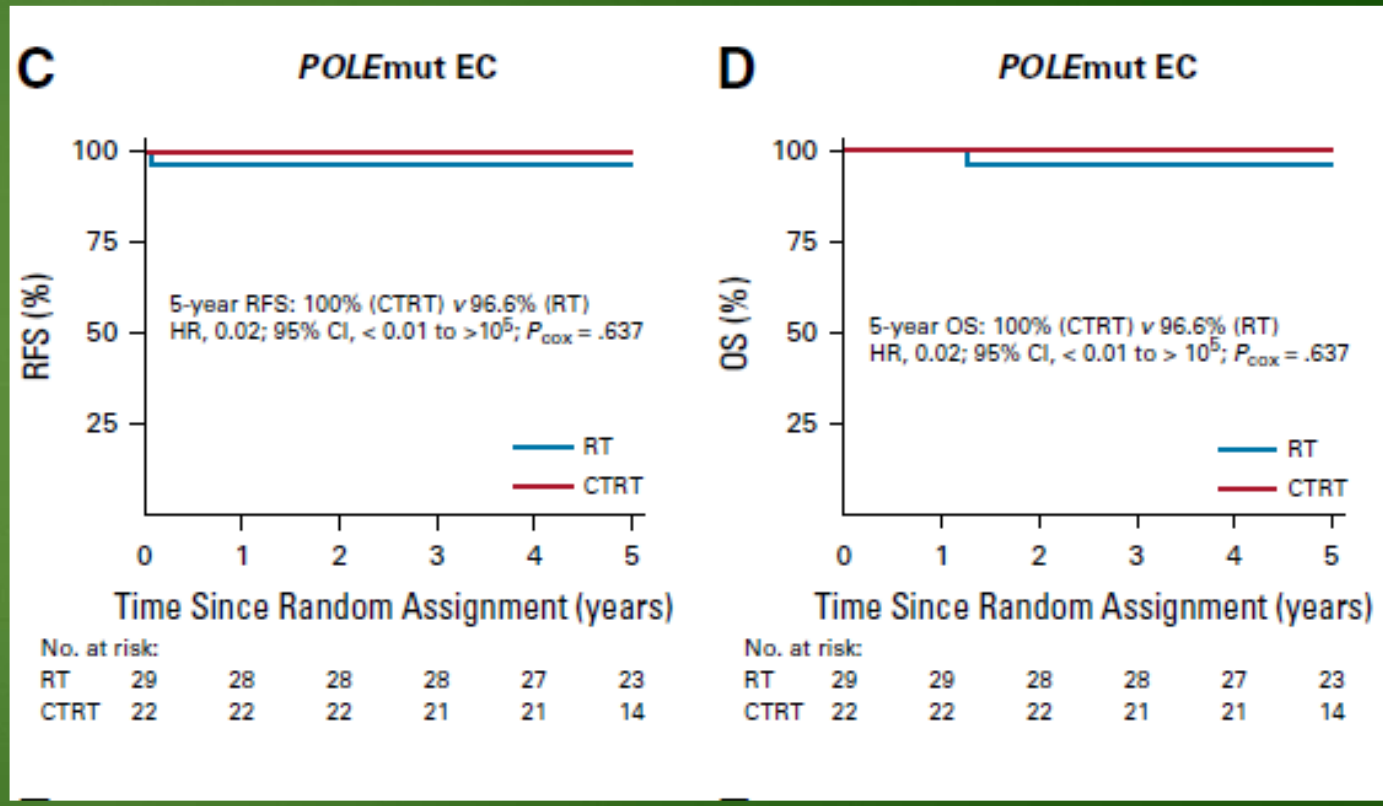


Van Gool et al. Clin Cancer Res. 2018

POLE-ultramutated endometrial carcinoma

- Applied molecular classification to PORTEC-3 trial cohort of 410 high-risk patients.
- **ECC (IAG3+LVSI, IBG3)**
- **ECC (II/III)**
- **Non-ECC (I/II/III)**

- Regardless of treatments (RT or CTRT), there were no differences in RFS and OS.



Leon-Castillo A. et al. J Clin Oncol 2020

POLE-ultramutated endometrial carcinoma

- Meta-analysis 359 endometrial cancers with *POLE*-mut, 294 (82%) were pathogenic.

- Apart from stage, other prognostic factors are not significantly associated with progression, recurrence, or death. Effects of adjuvant treatment were not associated with clinical outcome.

- Among the cases with pathogenic *POLE* mutations, adverse events (11 recurrence/progression, and 3 deaths) are rare. Salvage rates (8/11 ANED) are high.

McAlpine J. et al. Cancer 2021

POLE-ultramutated endometrial carcinoma

- Evidences so far indicate *POLE* mutants have favourable prognosis. Should be tested for routinely.

- Currently PORTEC4a prospective trial has incorporate molecular characteristics into high-intermediate risk patients (defined by traditional criteria) to determine if omission of adjuvant therapy or de-escalation treatment is safe or not.

Determining *POLE* mutational status

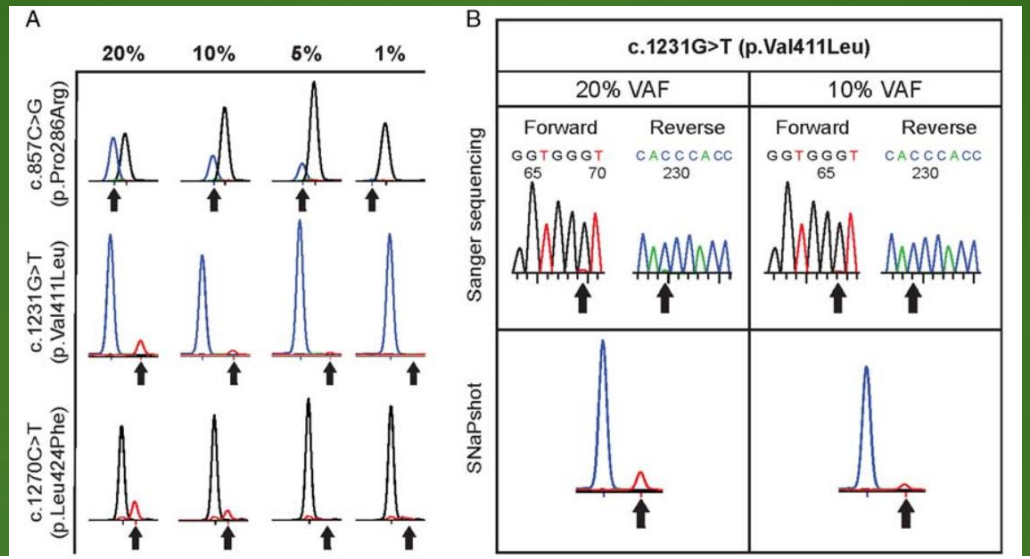


TABLE 2. *Evaluation of performance of SNaPshot sequencing, Sanger sequencing, and next-generation sequencing*

	SNaPshot	Sanger sequencing	NGS
Sensitivity	~10% VAF	~20% VAF	~5% VAF
Coverage	Target loci	Whole exon	Whole exon
Special equipment	Capillary electrophoresis	Capillary electrophoresis	NGS Sequencer
Interpretation	Easy	Intermediate	Intermediate
Molecular pathologist interpretation time	Minutes	Minutes to hours*	Minutes to hours*
Total time to results	Hours	Hours to days	Weeks
Estimated reagent cost per sample	$	$$	$$$

*Requires molecular pathologist to determine pathogenicity of novel variants.
NGS indicates next-generation sequencing; VAF, variant allele fraction.

Devereaux KA. et al. Mod Pathol. 2021
Devereaux KA. et al. Int J Gynecol Pathol. 2021

Determining pathogenicity of *POLE* mutation

- Leon-Castillo et al. described how analysis of (1) base changes, (2) TMB, (3) MSI status, and (4) *POLE* VAF by using six *in-silico* tools, a POLE score could be generated.

- *POLE* score ≥4 = pathogenic
- *POLE* score 3 = VUS
- *POLE* score ≤2 = non-pathogenic

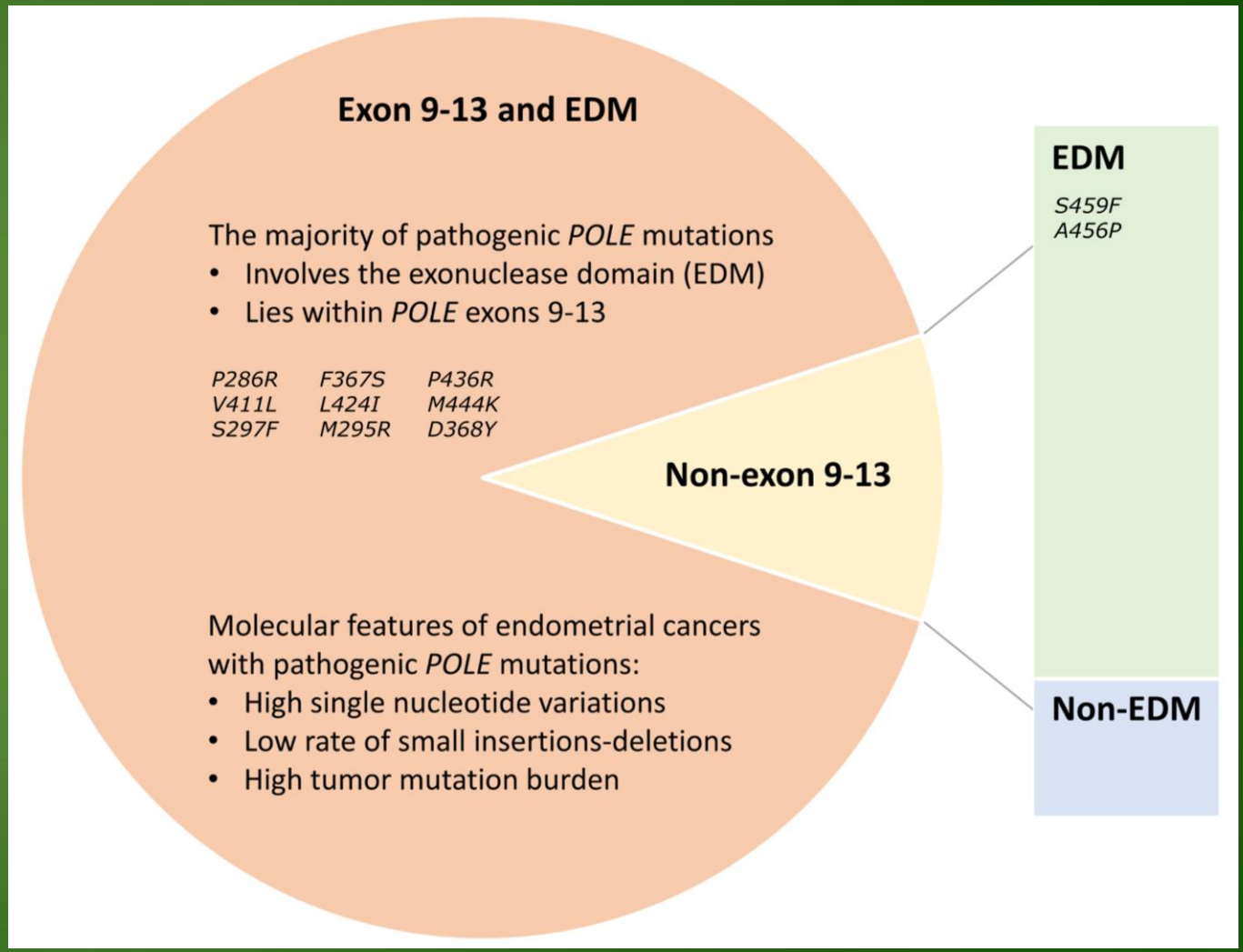
- Using these methods, the pathogenicity of novel *POLE* mutations discovered by NGS may be determined.

Leon-Castillo A. et al. J Path 2020

Determining pathogenicity of *POLE* mutation

- The majority of pathogenic *POLE* mutations are in the exonuclease domains. Only R705W mutation lies outside.

Protein change	Nucleotide substitution
P286R	c.857C>G
V411L	c.1231G>T/C
S297F	c.890C>T
S459F	c.1376C>T
A456P	c.1366G>C
F367S	c.1100T>C
L424I	c.1270C>A
M295R	c.884T>G
P436R	c.1307C>G
M444K	c.1331T>A
D368Y	c.1102G>T

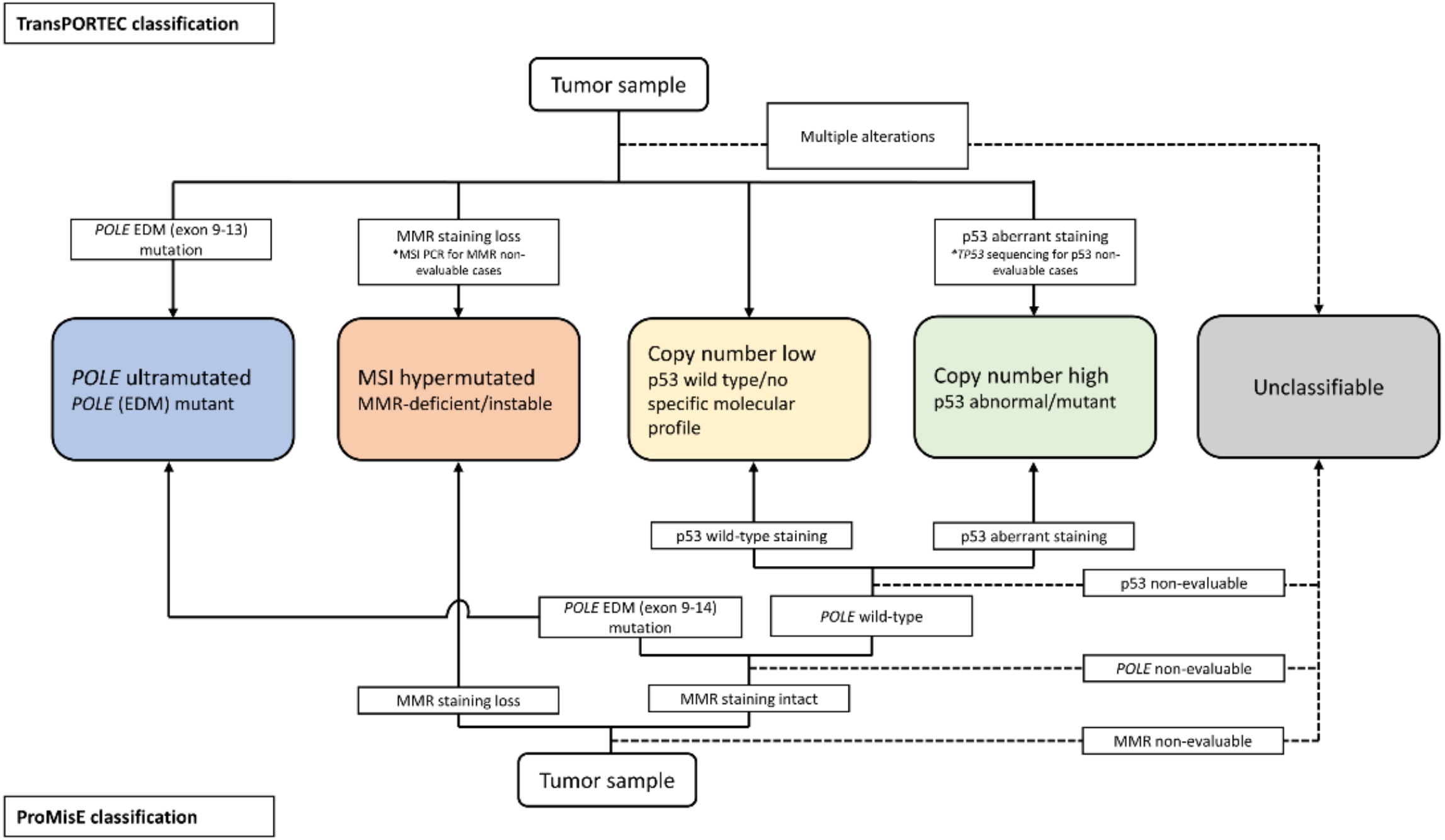


JJX Li and PPC Ip. Surge Pathol Clin. 2022
Leon-Castillo A. et al. J Path 2020

Incorporation of Molecular Classification of Endometrial Cancers – Practical issues

✓Surrogate markers: *POLE* mutational analysis, MMR IHC, and p53 IHC.

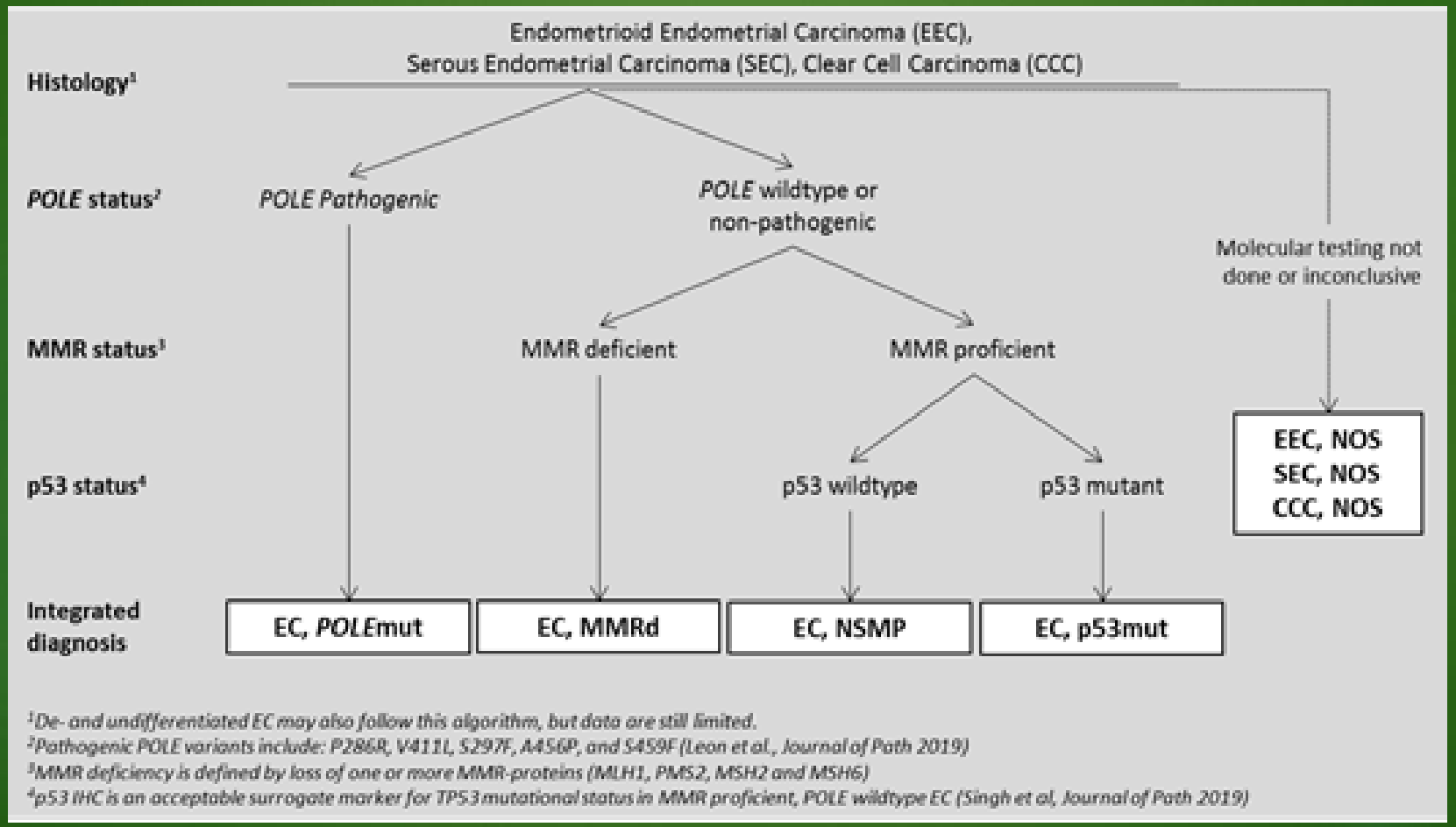
- Universal vs. selected groups of tumors?
- What is the appropriate algorithm for perform these tests?



JJX Li and PPC Ip. Surg Pathol Clin. 2022

Incorporation of molecular characteristics into endometrial cancer management

Lisa Vermij,[1] Vincent Smit,[1] Remi Nout[2] & Tjalling Bosse[1]
[1]*Department of Pathology, Leiden University Medical Center, and* [2]*Department of Radiation Oncology, Leiden University Medical Center, Leiden, the Netherlands*



[1]*De- and undifferentiated EC may also follow this algorithm, but data are still limited.*
[2]*Pathogenic POLE variants include: P286R, V411L, S297F, A456P, and S459F (Leon et al., Journal of Path 2019)*
[3]*MMR deficiency is defined by loss of one or more MMR-proteins (MLH1, PMS2, MSH2 and MSH6)*
[4]*p53 IHC is an acceptable surrogate marker for TP53 mutational status in MMR proficient, POLE wildtype EC (Singh et al, Journal of Path 2019)*

Vermij L. et al. Histopathology. 2020

Molecularly Classified Uterine FIGO Grade 3 Endometrioid Carcinomas Show Distinctive Clinical Outcomes But Overlapping Morphologic Features

Amy Joehlin-Price, MD, Jessica Van Ziffle, PhD,† Nancy K. Hills, MA, PhD,‡ Nicholas Ladwig, MD,† Joseph T. Rabban, MD, MPH,† and Karuna Garg, MD†*

TABLE 4. Clinicopathologic and Molecular Features of Cases Showing Multiple Molecular Classifying Features

	Age (y)	*POLE*	MMR IHC	p53 IHC	Lynch Status	FIGO Stage	Adjuvant Therapy	Follow-up
1	63	p.P286R	PMS2 loss	Wild-type	Unknown	IB	None	NED (24 mo)
2	55	p.P286H	MSH2/MSH6 loss	Wild-type	*MSH6* germline mutation	IA	None	NED (15 mo)
3	56	p.M444K	MLH1/PMS2 loss	Wild-type	Unknown	IIIC2	None	NED (100 mo)
4	59	p.M444K	PMS2 loss	Aberrant (diffuse)	Unknown	IA	None	NED (134 mo)
5	63	p.P286R	Intact	Aberrant (null)	Not applicable	IB	None	NED (10 mo)
6	59	None	PMS2 loss	Aberrant (diffuse)	Unknown	IA	None	NED (119 mo)

NED indicates no evidence of disease.

- 6 Multiple classifiers
- Vermij: POLE first, missed patient with Lynch
- ProMisE: MMR first, missed POLE

Joehlin-Price A. et al. Am J Surg Pathol. 2021

Molecular Classification of Endometrial Cancers – Multiple Classifiers

- Multiple classifiers (more than one molecular profile).

- MMRd+p53abn
- *POLE*mut+p53abn
- *POLE*mut+MMRd
- *POLE*mut+MMRd+p53abn

Journal of Pathology
J Pathol 2020; **250:** 312–322
Published online 12 January 2020 in Wiley Online Library
(wileyonlinelibrary.com) DOI: 10.1002/path.5373

ORIGINAL PAPER

Clinicopathological and molecular characterisation of 'multiple-classifier' endometrial carcinomas

Alicia León-Castillo[1], Ester Gilvazquez[2,3], Remi Nout[4], Vincent THBM Smit[1], Jessica N McAlpine[5], Melissa McConechy[6], Stefan Kommoss[7], Sara Y Brucker[7], Joseph W Carlson[8], Elisabeth Epstein[9], Tilman T Rau[10], Robert A Soslow[11], Raji Ganesan[12], Xavier Matias-Guiu[13], Esther Oliva[14], Beth T Harrison[15], David N Church[2,3], C Blake Gilks[16] and Tjalling Bosse[1]*

Journal of Pathology
J Pathol 2020; **250:** 323–335
Published online 30 January 2020 in Wiley Online Library
(wileyonlinelibrary.com) DOI: 10.1002/path.5372

ORIGINAL PAPER

Interpretation of somatic *POLE* mutations in endometrial carcinoma

Alicia León-Castillo[1†], Heidi Britton[2†], Melissa K McConechy[3], Jessica N McAlpine[4], Remi Nout[5], Stefan Kommoss[6], Sara Y Brucker[6], Joseph W Carlson[7], Elisabeth Epstein[8], Tilman T Rau[9], Tjalling Bosse[1*‡], David N Church[10,11] and C Blake Gilks[12]

Molecular Classification of Endometrial Cancers – Multiple Classifiers

- Multiple classifiers (more than one molecular profile).

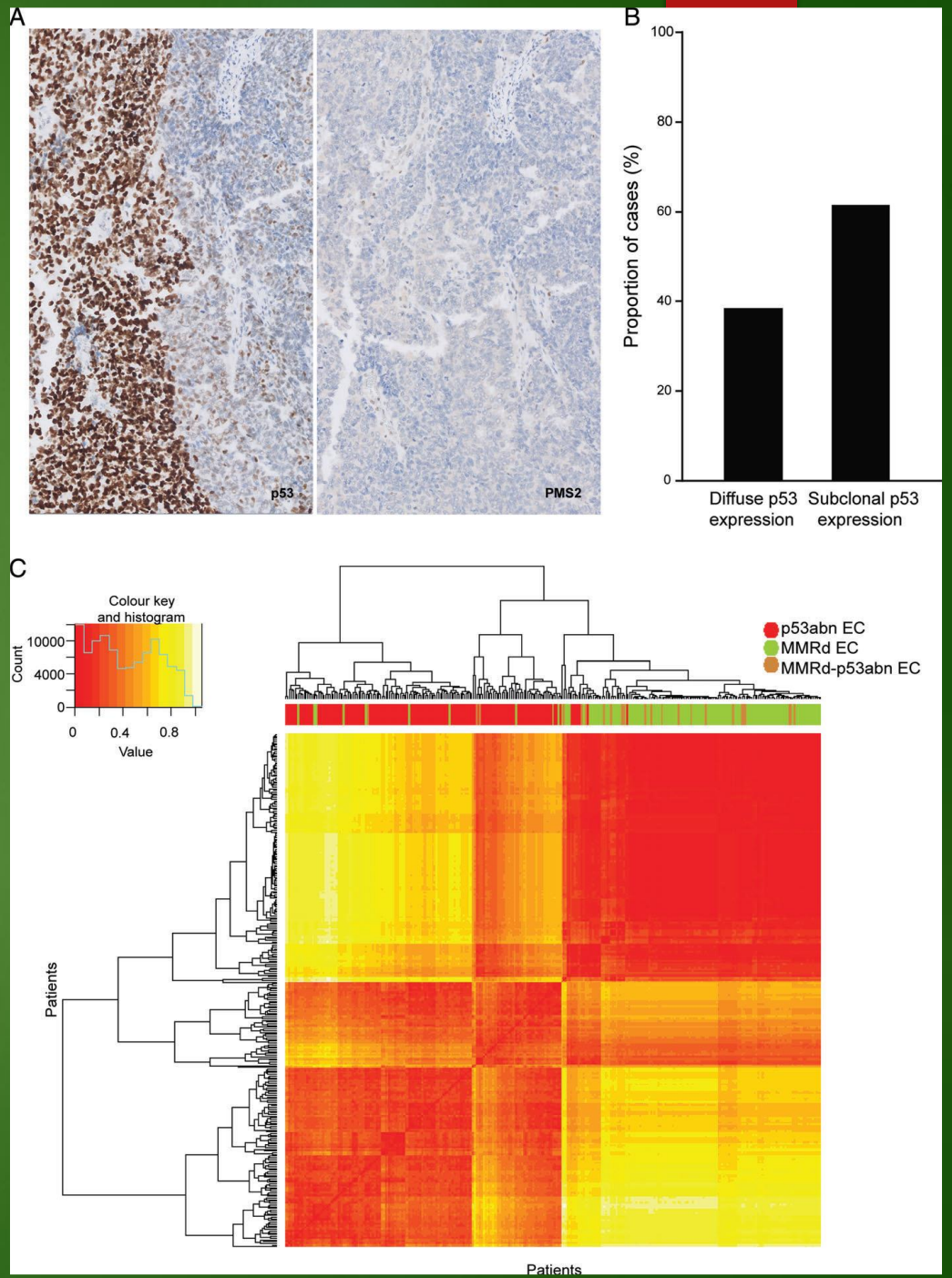
- Leon-Castillo: 3518 EC cases, 107 (3%) are multiple classifiers

- 64/107 (60%) = MMRd+p53abn
- 31/107 (29%) = *POLE*mut+p53abn
- 12/107 (11%) = *POLE*mut+MMRd+p53abn

Leon-Castillo A. et al. J Pathol 2020

MMRd+p53abn EC

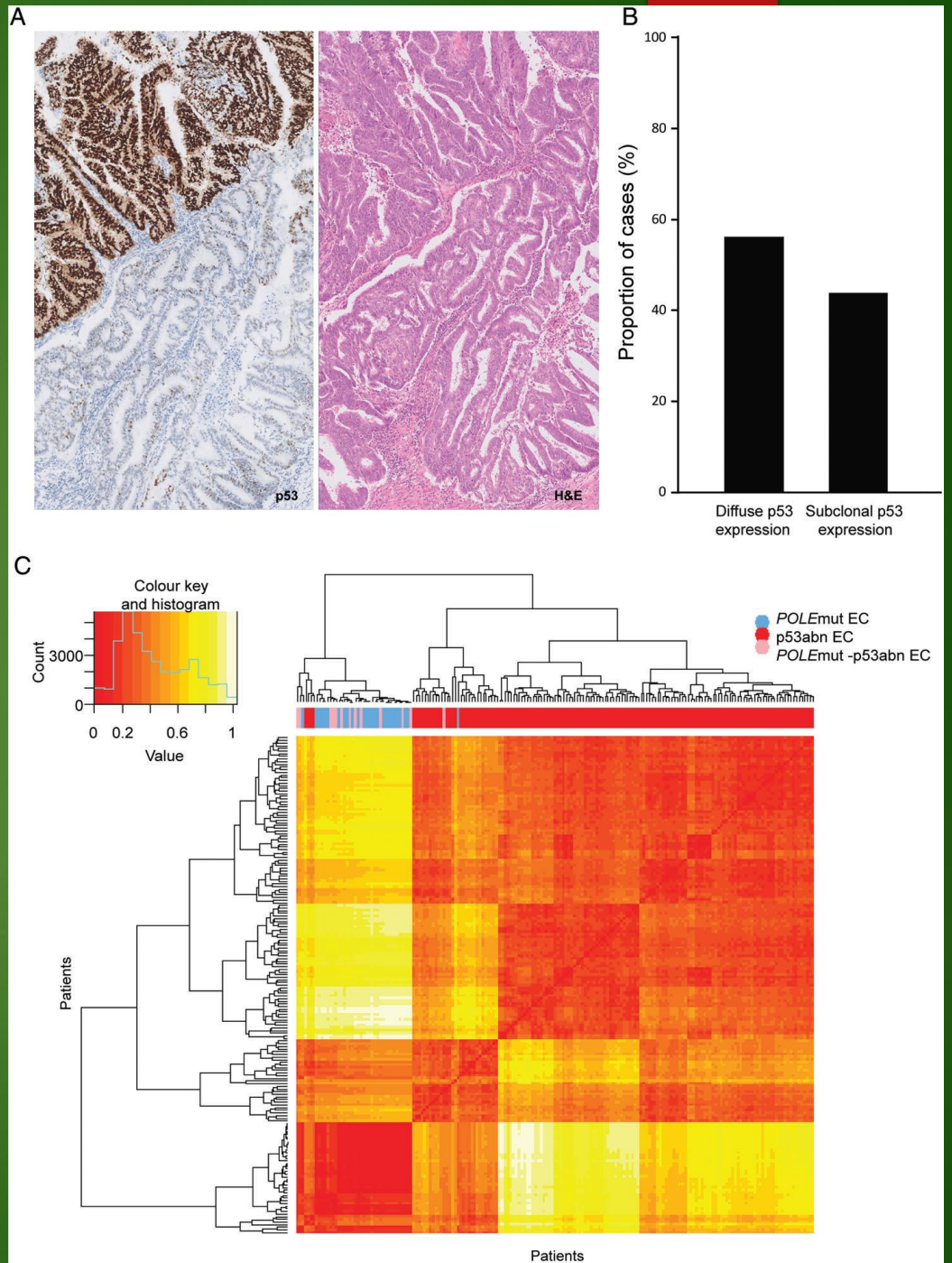
- Stage IA/IB (~73.5%).
- FIGO grade 3 endometrioid or mixed carcinomas (84.4%).
- Hierarchical clustering by SNVs and SCNAs showed that they clustered with MMRd, rather than with p53abn.
- RFS for stage I: MMRd+p53abn (92.2%) vs. p53abn only (70.8%).



Leon-Castillo A. et al. J Pathol 2020

*POLE*mut+p53abn EC

- Stage IA/IB (77.4%).
- FIGO grade 3 endometrioid or mixed carcinomas (90.4%).
- Hierarchical clustering by SNVs and SCNAs showed that they clustered with *POLE*mut, rather than with p53abn.
- RFS for stage I: *POLE*mut+p53abn (94.1%) vs. p53abn only (70.8%).



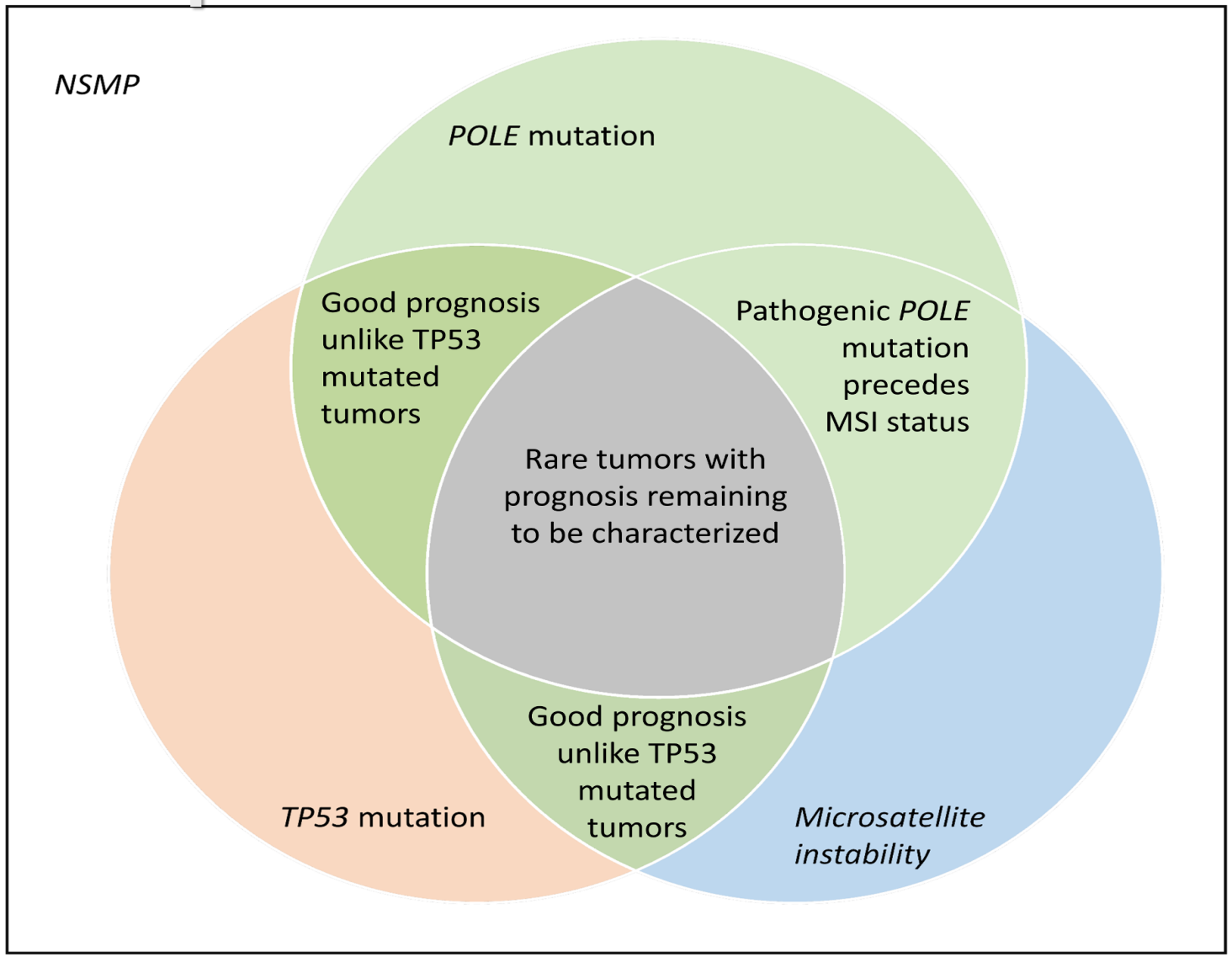
Leon-Castillo A. et al. J Pathol 2020

*POLE*mut+MMRd EC

- Leon-Castillo: 3361 EC cases, 13 (0.004%) were *POLE*mut+MMRd.
- Genomically similar to pure *POLE*-mut .
- Prognostically similar to *POLE*mut (RFS 92.3%).
- Non-pathogenic *POLE*mut+MMRd with RFS 76.2% (similar to MMRd, *POLE*-wild type).

Leon-Castillo A. et al. J Pathol 2020

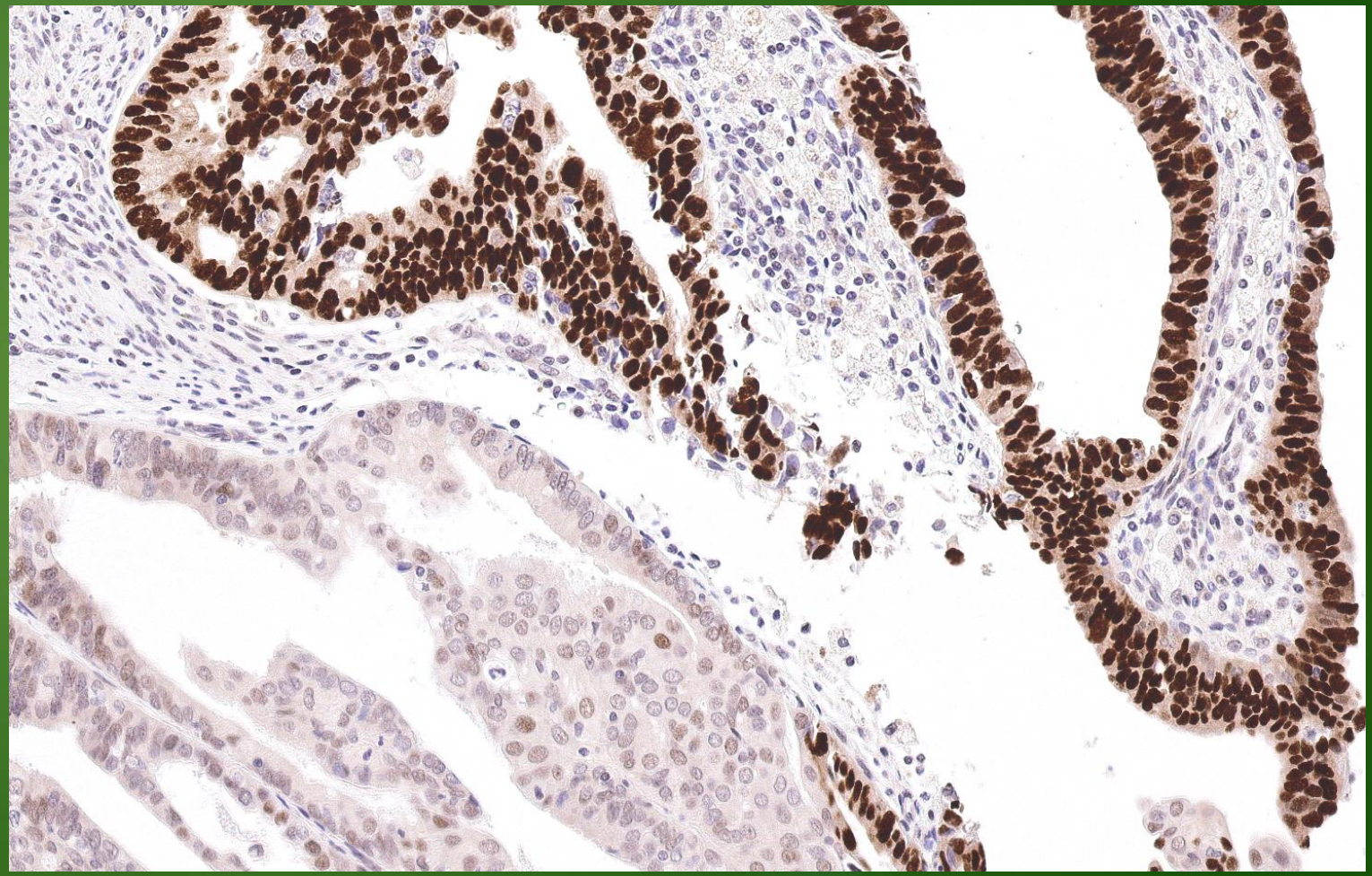
Multiple Molecular Classifiers



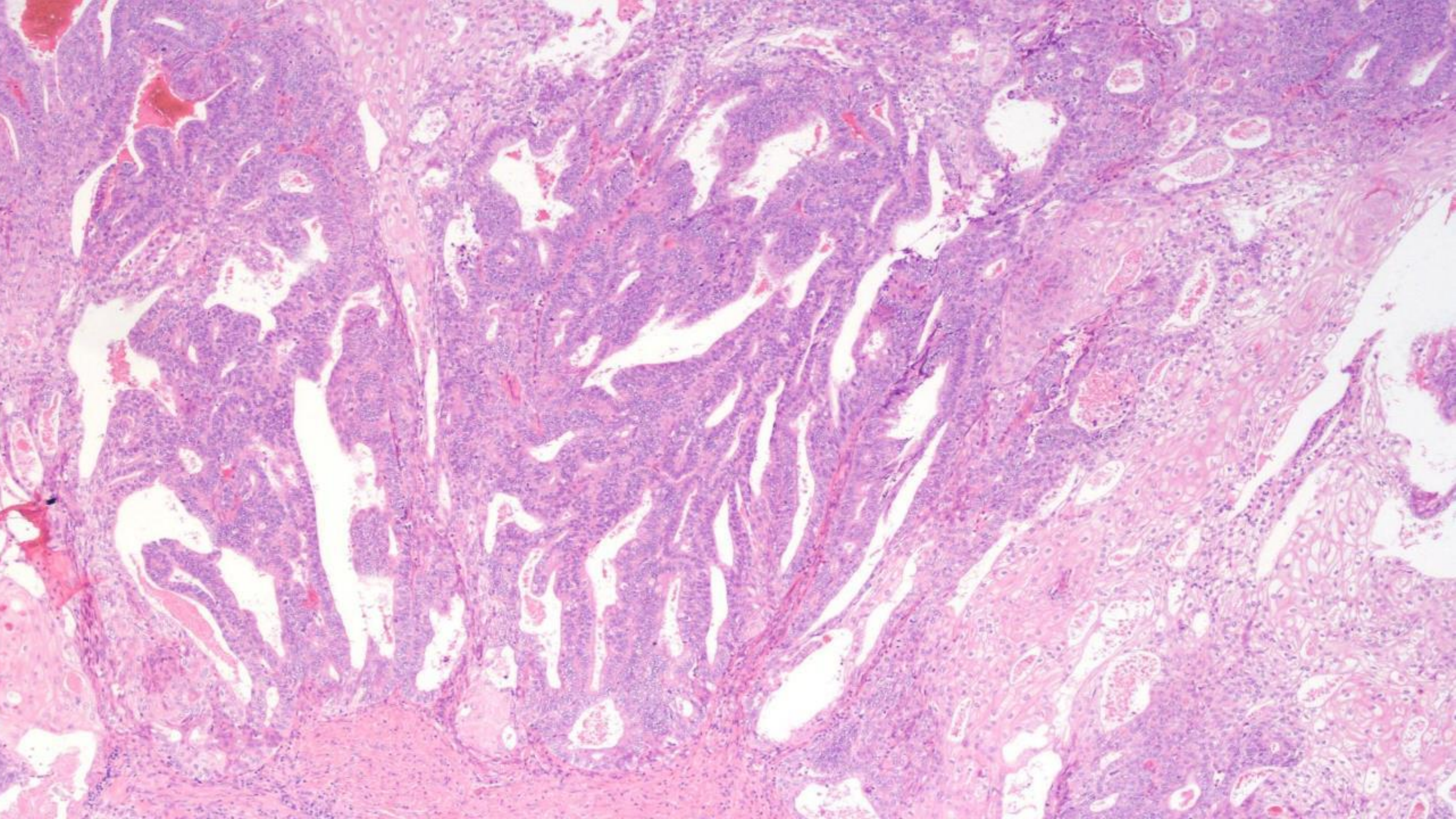
JJX Li. and PPC Ip. Surg Pathol Clin. 2022

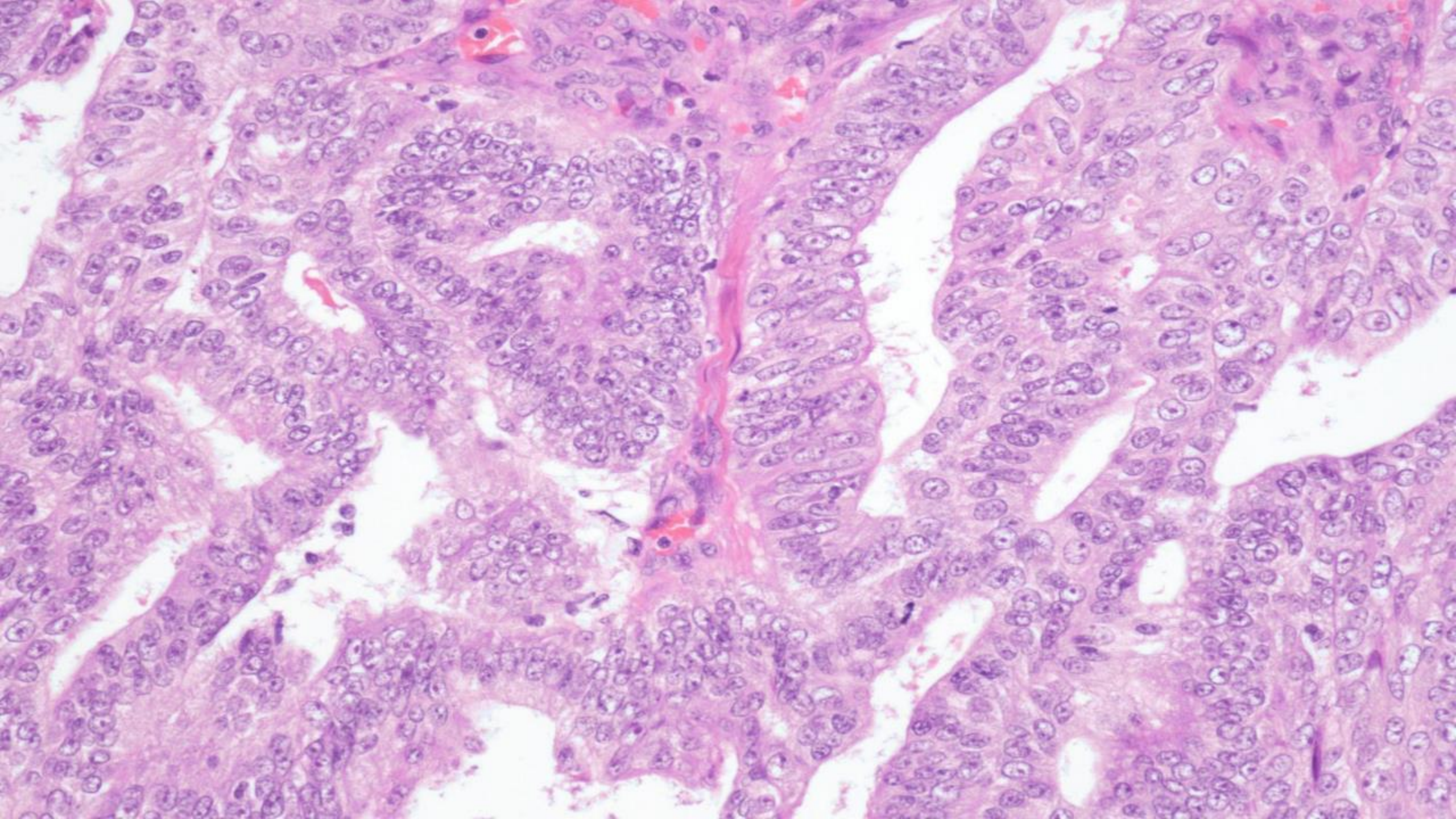
Subclonal expression pattern in Immunohistochemistry

- Indicates mixed classifiers (>10% of tumor cells with a second pattern of staining):
- POLE mutants with wild-type p53 and/or distinct abnormal p53.
- POLE mutants with distinct MMRd.
- MMRd with abnormal p53.



JJX Li and PPC Ip. Surg Pathol Clin. 2022





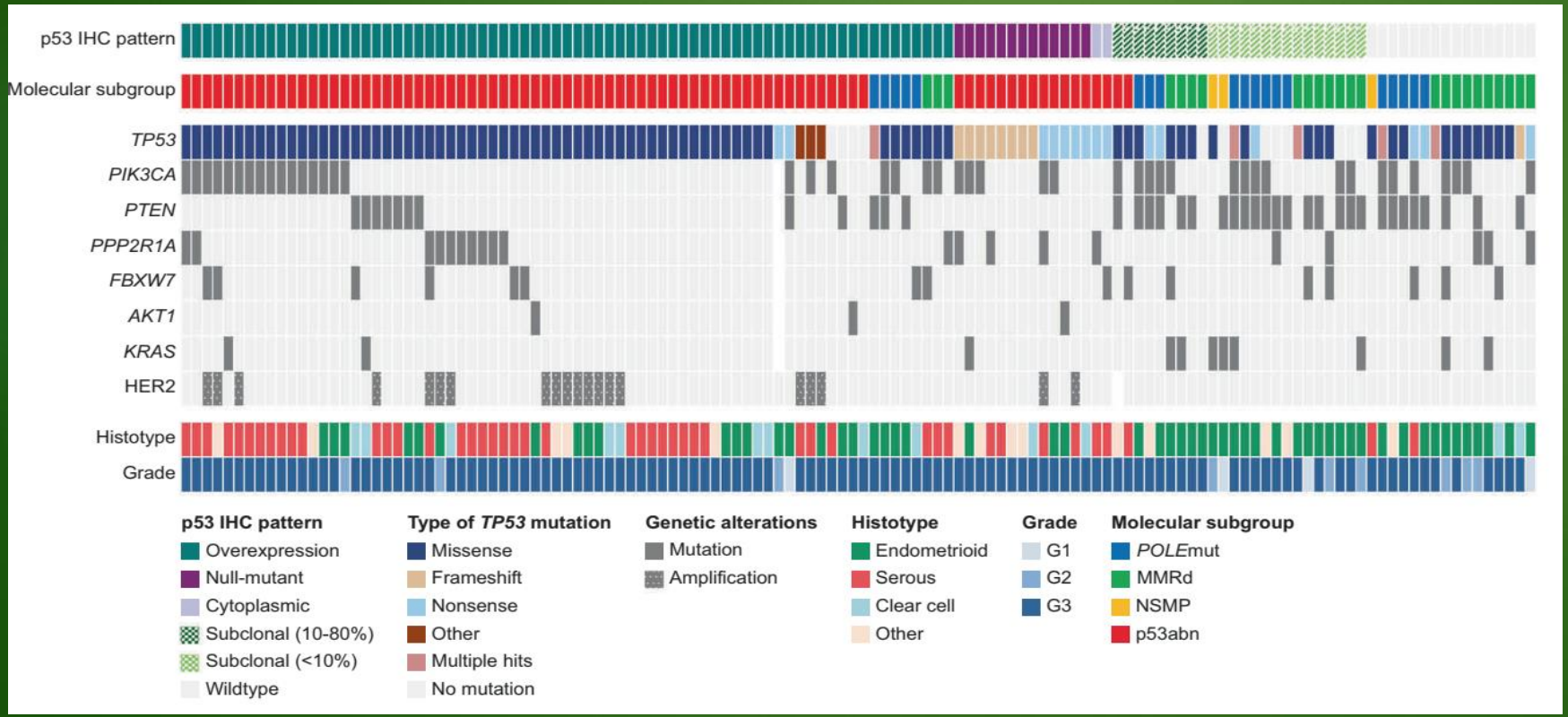
Low-grade Low-stage Endometrial Endometrioid Carcinoma

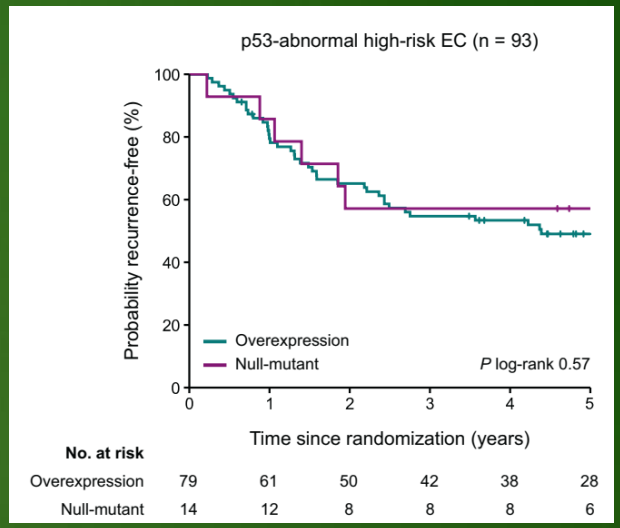
- FIGO low-grade, FIGO stage I disease is associated with >90% five-year survival.
- The risk-stratification models does not provide a completely accurate prognostication in some. Three to 6% patients developed recurrence at a median of 48 months.
- Important factors other than histotyping and grading: ***TP53***, ***CTNNB1***, **L1-CAM, 1q gain.**

Siegel RL. et al. CA A Cancer J Clin 2021
Lu KH. et al. N Eng J Med. 2020
Jemal A. et al. J Natl Cancer Inst. 2017
Murali R. et al. Lancet Oncol. 2014

Factors associated with early recurrence in low-grade low-stage Endometrioid Ca: *TP53*

- In the literature, 2-15% of **low-grade** endometrioid carcinoma are p53abn.
- Regardless of histotype, patients with p53abn had poorer outcome (PORTEC-3 finding).





Vermij L. et al Mod Pathol. 2022
Thompson EF. et al. Mod Pathol 2022
Safdar NS. et al. J Natl Cancer Inst. 2022
Vermij L. Histopathology 2020
Leon-Castillo A. et al. J Clin Oncol 2020
Yano M. et al. Modern Pathol 2019
Wortman BG. et al. Cancer 2018
Stelloo E. et al. Clin Cancer Res 2016

Factors associated with early recurrence in low-grade low-stage Endometrioid Ca: *TP53*

- In 6% of cases in the PORTEC 1 and 2 trials (n=881), and >2500 cases from Canada cohort, low-grade stage I endometrioid Ca were abnormal by p53 immunostain.

- Interobserver agreement by expert Gyn pathologists on ‘low-grade endometrioid carcinoma’ was not perfect, has potential to exclude conducting of p53 immunostains (if not universally performed).

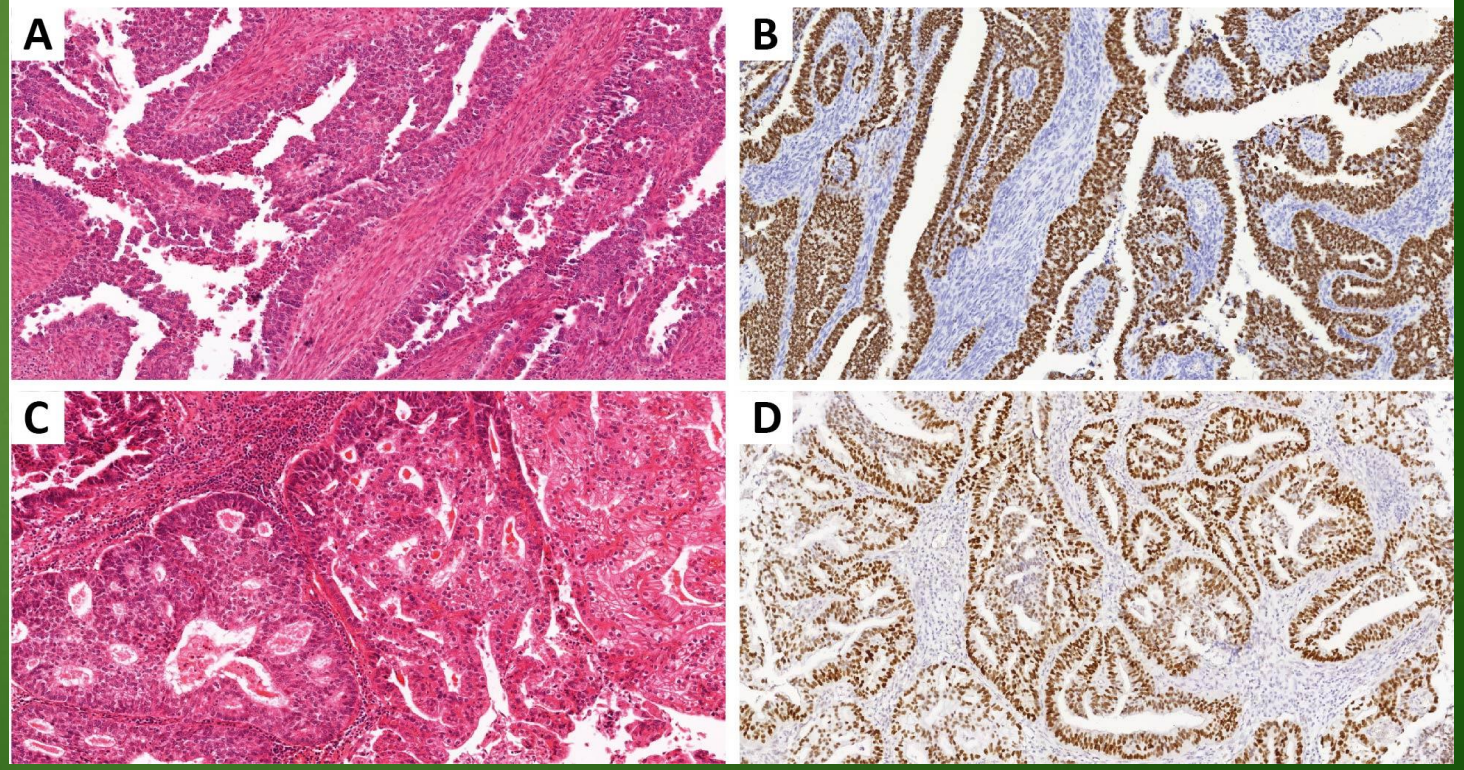
Vermij L. et al. Lab Invest. S995-996 [Abstract 982] 2023
Vermij L. et al. Histopathology 2020
Leon-Castillo A. et al. J Clin Oncol 2020
Stelloo E. et al. Clin Cancer Res 2016
Wortman BG. et al. Cancer 2018
Yano M. et al. Modern Pathol 2019

Factors associated with early recurrence in low-grade low-stage Endometrioid Ca: *TP53*

- Recognition of abnormal p53 (and/or underlying *TP53* mutations) would enable classification into TCGA group 4 and option of adjuvant therapy.

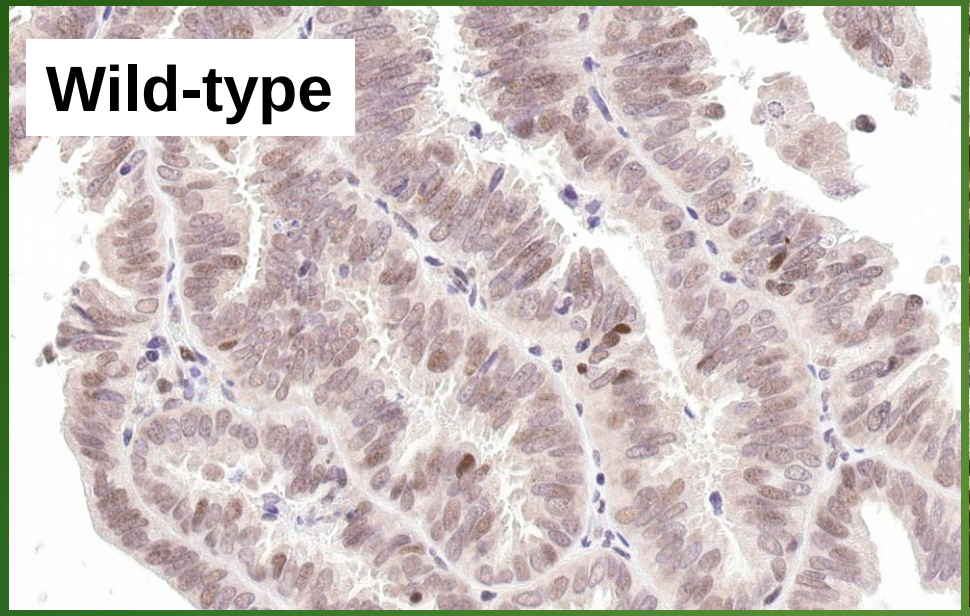
- Rationale for prospective trial in PORTEC4a (observation, escalation to vaginal brachytherapy, or to external beam RT).

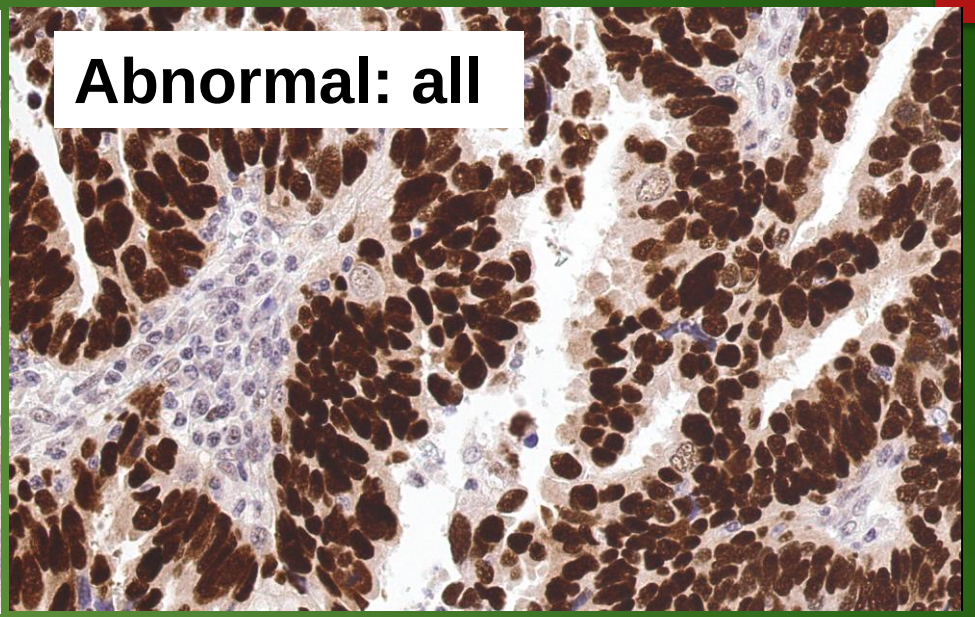
Figure 1. Representative H&E and p53 immunohistochemistry images of a case which none of the expert pathologists classified as low-grade endometrioid endometrial carcinoma (EEC) (A, B) and a case assigned as low-grade EEC by 5 out of 6 expert pathologists (C, D). All images taken at x10 magnification.

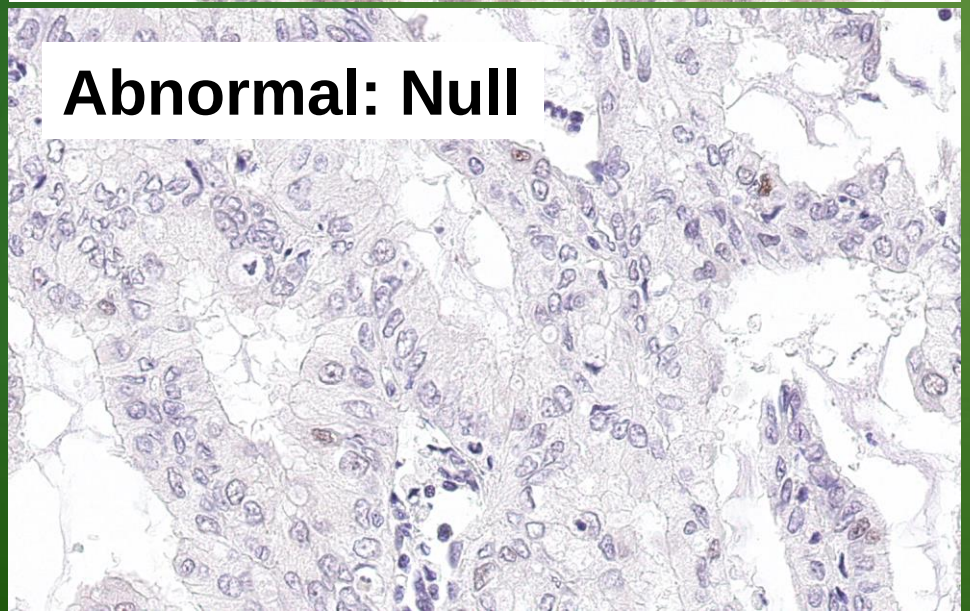


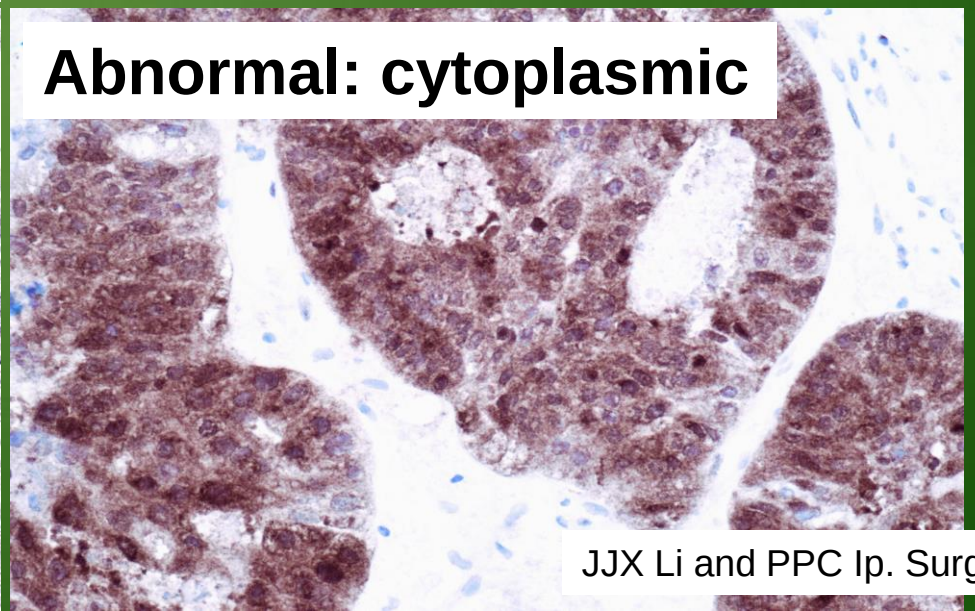
*Vermij L. et al. Lab Invest. S995-996 [Abstract 982] 2023
Thompson EF. et al. Mod Pathol 2022
Safdar NS. et al. J Natl Cancer Inst. 2022

Reporting p53 immunohistochemistry









JJX Li and PPC Ip. Surg Pathol Clin. 2022

Reporting p53 immunohistochemistry

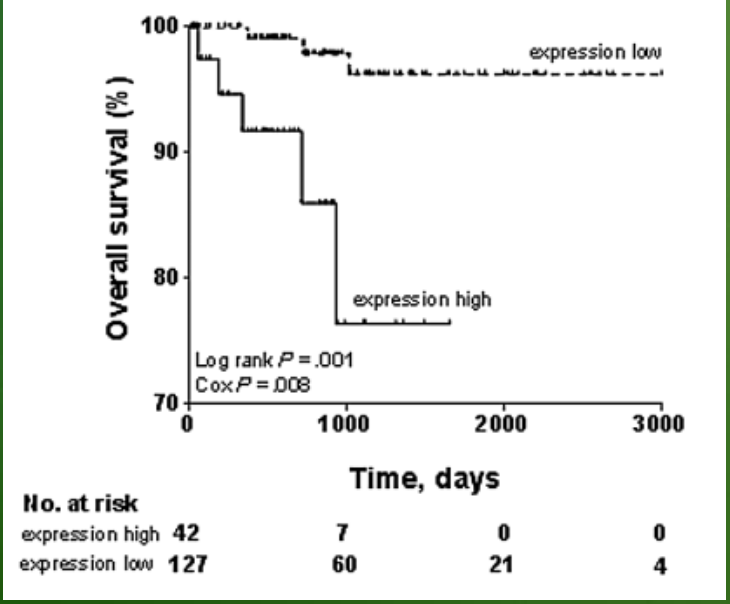
Never report p53 as positive or negative.
Communication unclear!

JJX Li and PPC Ip. Surg Pathol Clin. 2022

Factors associated with early recurrence in low-grade low-stage Endometrioid Ca: *CTNNB1*

- Mutations in the Wnt pathway, including *CTNNB1*, have been found to be associated with carcinogenesis in different cancer types.

- *CTNNB1* exon 3 mutations enriched in TCGA endometrial carcinoma, NSMP, has been shown to associate with worse overall survival.



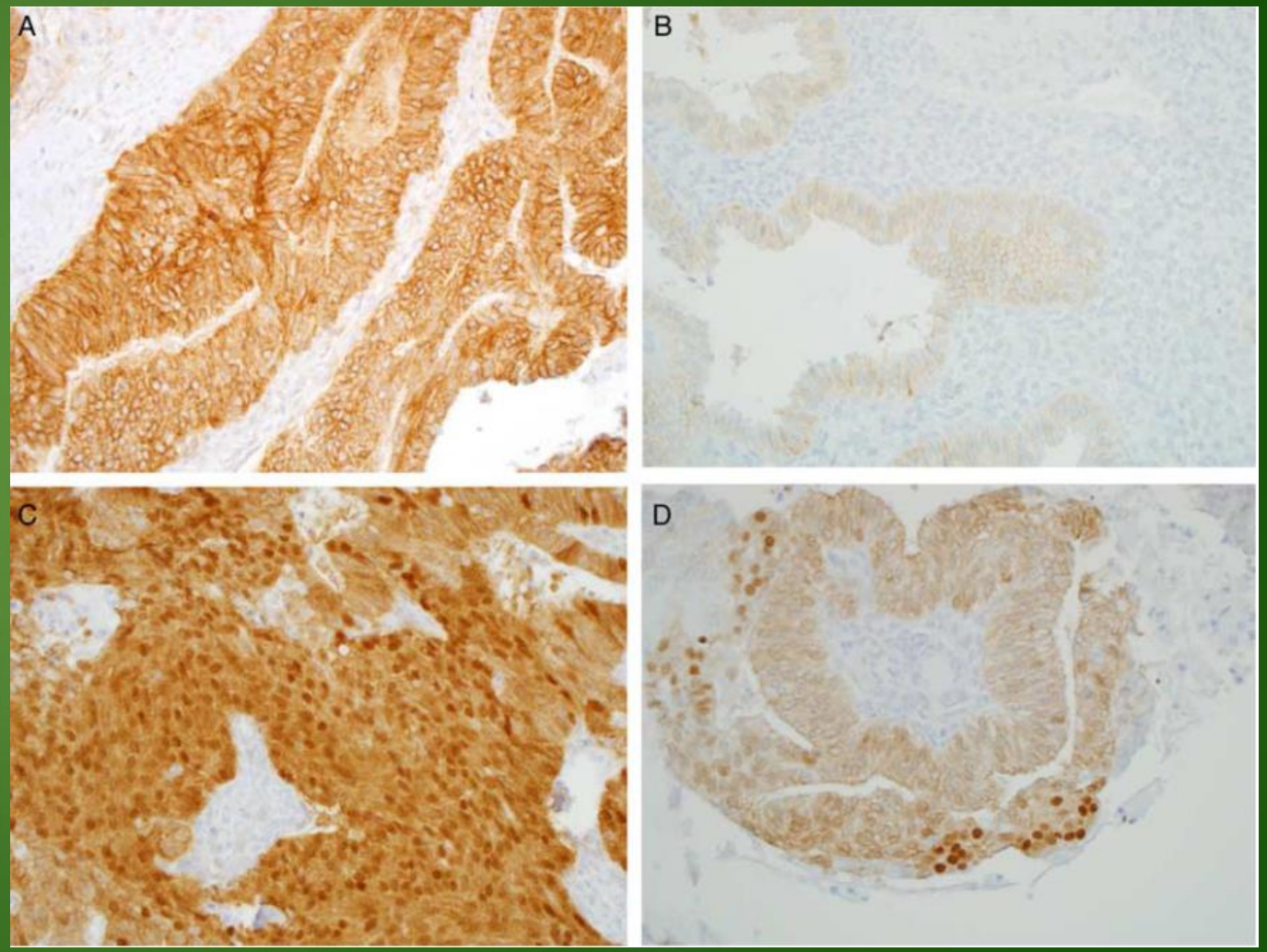
Liu Y. et al

Matrai CE. et al. Int J Gynecol Pathol. 2021
Costigan DC et al. Int J Gynecol Pathol. 2019
Moroney MR. et al. Gynecol Oncol. 2019
Kurnit KC. et al Mod Pathol. 2017
Stelloo E. et al. Clin Cancer Res. 2016
Myres A. et al. Gynecol Oncol. 2014
Liu Y. et al J Natl. Cancer Inst. 2014

β-catenin immunohistochemistry as a surrogate marker for *CTNNB1* mutation

	Sensitivity	Specificity	PPV	NPV
Any CTNNB1	82%	90%	89%	84%
CTNNB1 exon 3	91%	89%	86%	93%

- Nuclear β-catenin was significantly associated with underlying *CTNNB1* mutation (p<0.0001).
- Criteria for positive staining not well-established (positive staining can ranged from 5 – 60%).

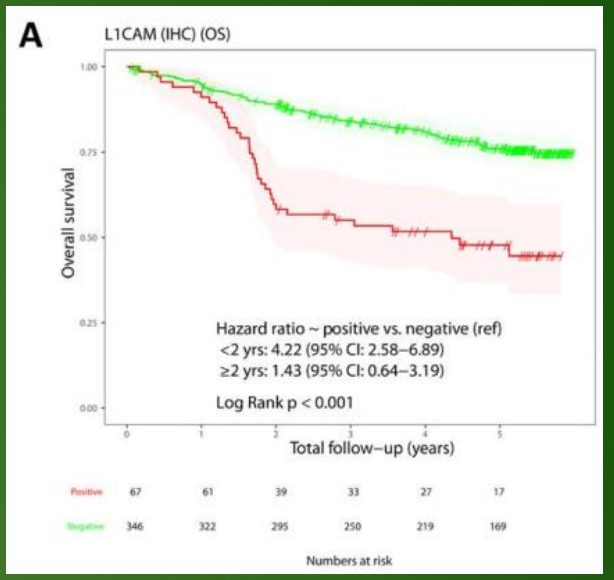


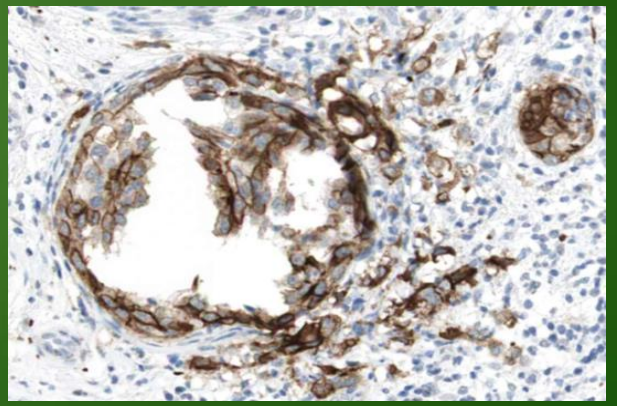
Costigan DC et al. Int J Gynecol Pathol. 2019

Factors associated with early recurrence in low-grade low-stage Endometrioid Ca: L1CAM

- **L1CAM (**L1-cell adhesion molecule): transmembrane protein of the immunoglobulin family, expression associated with an aggressive behavior. In endometrial Ca activates Wnt signalling and epithelial–mesenchymal transition (EMT).

- L1CAM overexpression (>10%) associated with older age, lower body mass index (BMI), advanced stage, grade 3, and non-endometrioid histology. ?attributed to tumors with *TP53* mutations.

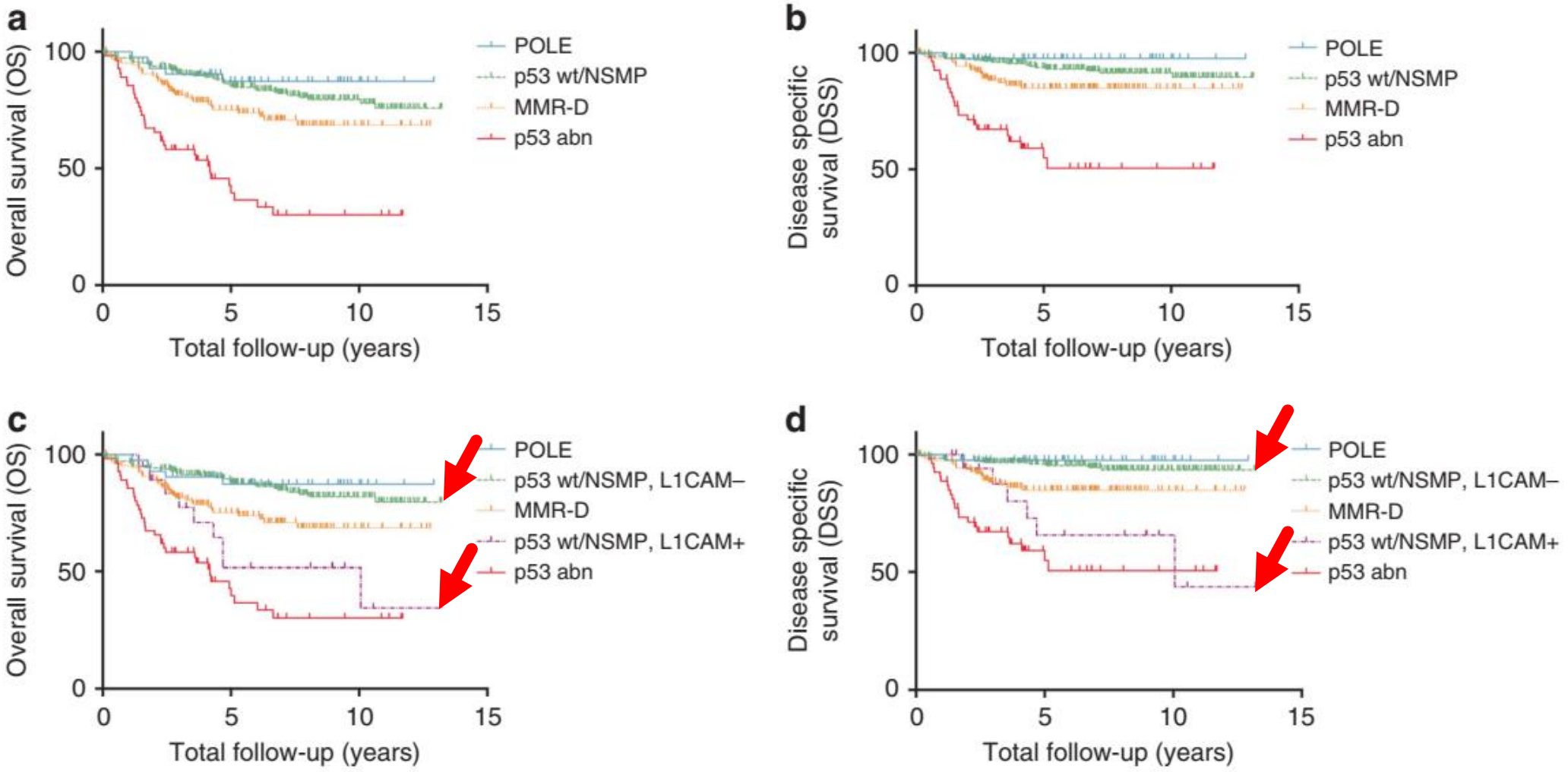




Karnezis AN. et al. J Pathol. 2017
Stelloo E. et al. Clin Cancer Res. 2016

L1CAM further stratifies endometrial carcinoma patients with no specific molecular risk profile

Felix KF Kommoss[1], Anthony N. Karnezis[2], Friedrich Kommoss[3], Aline Talhouk[2], Florin-Andrei Taran[4], Annette Staebler[5], C. Blake Gilks[6], David G. Huntsman[2], Bernhard Krämer[4], Sara Y. Brucker[4], Jessica N. McAlpine[7] and Stefan Kommoss[4]



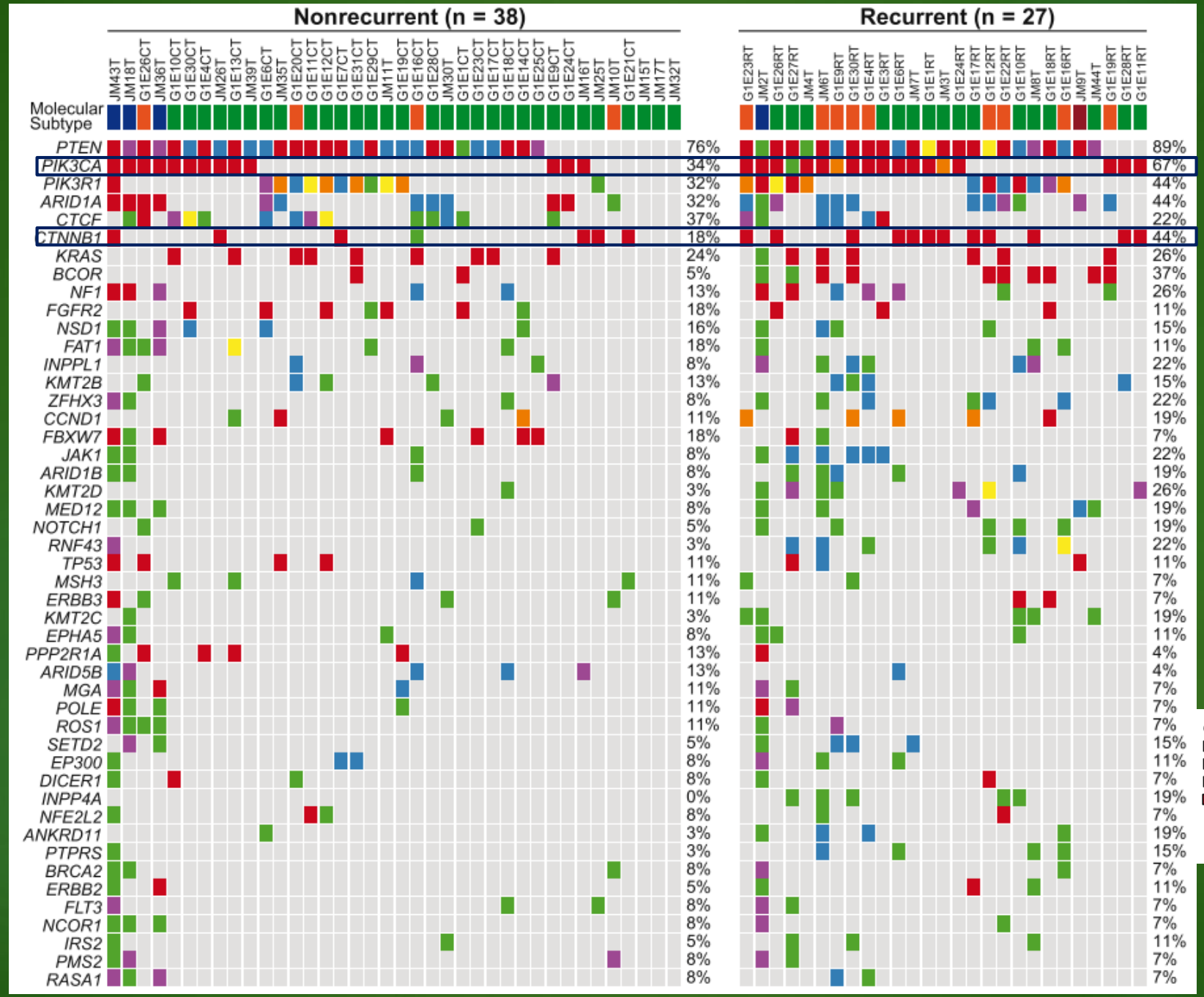
Kommoss FKF. et al. Br J Cancer 2018

Genomic Determinants of Early Recurrences in Low-Stage, Low-Grade Endometrioid Endometrial Carcinoma

Nida S. Safdar, MD,[1,†] Marina Stasenko, MD,[2,3,†] Pier Selenica, BSc,[4] Axel S. Martin, MSc,[5] Edaise M. da Silva, PhD,[4] Ana Paula Martins Sebastiao, MD,[4,6] Melissa Krystel-Whittemore, MD,[1,4] Nadeem R. Abu-Rustum, MD,[2] Jorge S. Reis-Filho, MD, PhD, FRCPath,[4] Robert A. Soslow, MD,[4] Ronglai Shen, PhD,[5] Jennifer J. Mueller, MD,[2,‡] Esther Oliva, MD,[1,‡] Britta Weigelt, PhD [4,*,‡]

- FIGO grade 1, FIGO stage IA/B endometrioid Ca.
- No lymphovascular space invasion.
- No postoperative adjuvant therapy.
- Developed biopsy-proven recurrence ≥36 months.
- 65 cases – whole exome sequencing.

Safdar NS. et al. JNCI J Natl Cancer Inst. 2022



Safdar NS. et al. JNCI J Natl Cancer Inst. 2022

Factors associated with early recurrence in low-grade low-stage Endometrioid Ca

Univariate analysis	P-value
Age	<0.001
BMI	<0.001
Positive/negative peritoneal cytology	0.032
ProMisE subtyping	0.043
PIK3CA	0.02
CTNNB1 hotspot	0.046
Chromosome 1q gain	0.002

Safdar NS. et al. JNCI J Natl Cancer Inst. 2022

Factors associated with early recurrence in low-grade low-stage Endometrioid Ca

Multivariate analysis	P-value
Age	0.2
BMI	0.6
Positive/negative peritoneal cytology	-
ProMisE subtyping (MMRd)	0.02
PIK3CA	0.01
CTNNB1 hotspot	0.14
Chromosome 1q gain	0.02

- Validated in an independent set of 32 FIGO grade 1, stage 1 EEC from TCGA
- The only factor associated with recurrence is **chromosome 1q gain**.

Safdar NS. et al. JNCI J Natl Cancer Inst. 2022

Factors associated with early recurrence in low-grade low-stage Endometrioid Ca: *1q gain*

- Chromosome 1q gains have been associated with adverse outcomes in multiple tumor types (e.g. pediatric brain tumors, multiple myeloma) and in female reproductive tract, mesonephric and mesonephric-like carcinomas.

- In endometrial carcinoma, 1q32.1 amplification and/or 1q high-level gain has been identified as a marker of poor clinical outcome.

Momeni-Boroujeni A. et al. Mod Pathol. 2022

Da Silva EM. et al. Mod Pathol. 2021

Na K. et al. Am J Surg Pathol. 2019

Mirkovic J. et al. Am J Surg Pathol. 2018

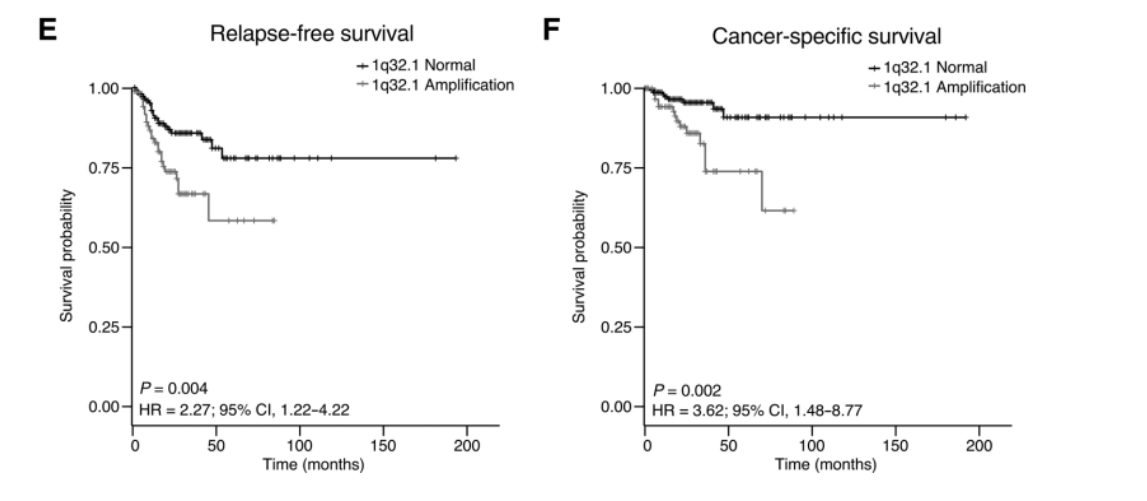
Depreeuw J. et al. Clin Cancer Res. 2017

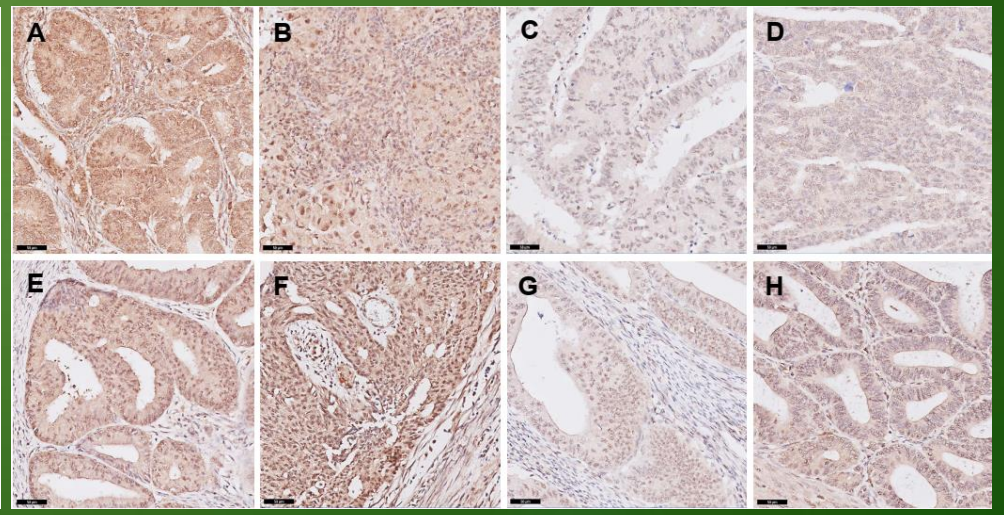
Mirkovic J. et al. Mod Pathol. 2015

Amplification of 1q32.1 Refines the Molecular Classification of Endometrial Carcinoma

Jeroen Depreeuw[1,2,3], Ellen Stelloo[4], Elisabeth M. Osse[4], Carien L. Creutzberg[5], Remi A. Nout[5], Matthieu Moisse[2,3], Diego A. Garcia-Dios[1,2,3], Michael Dewaele[6,7], Karen Willekens[6,7], Jean-Christophe Marine[6,7], Xavier Matias-Guiu[8], Frédéric Amant[1,9], Diether Lambrechts[2,3], and Tjalling Bosse[4]

- Analysis of somatic copy number alterations in 141 cases (Belgium and Spain).
- Validated with 973 TCGA data PORTEC-1 and PORTEC-2 trials.
- Chromosome 1q32.1 gain drives *MDM4* (↑mRNA).

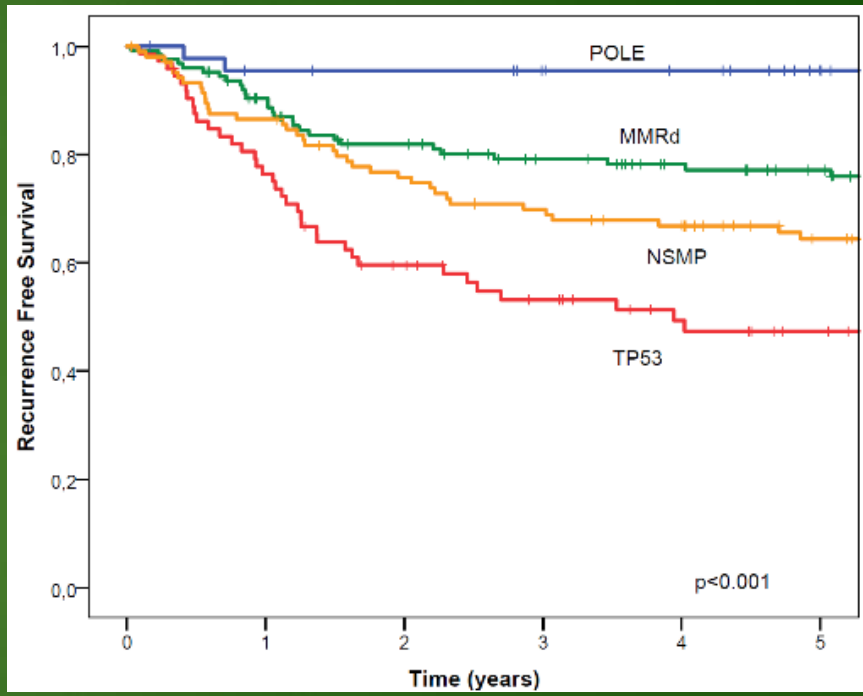




Depreeuw J. et al. Clin Cancer Res. 2017

Endometrial Ca, No Specific Molecular Profile (NSMP)

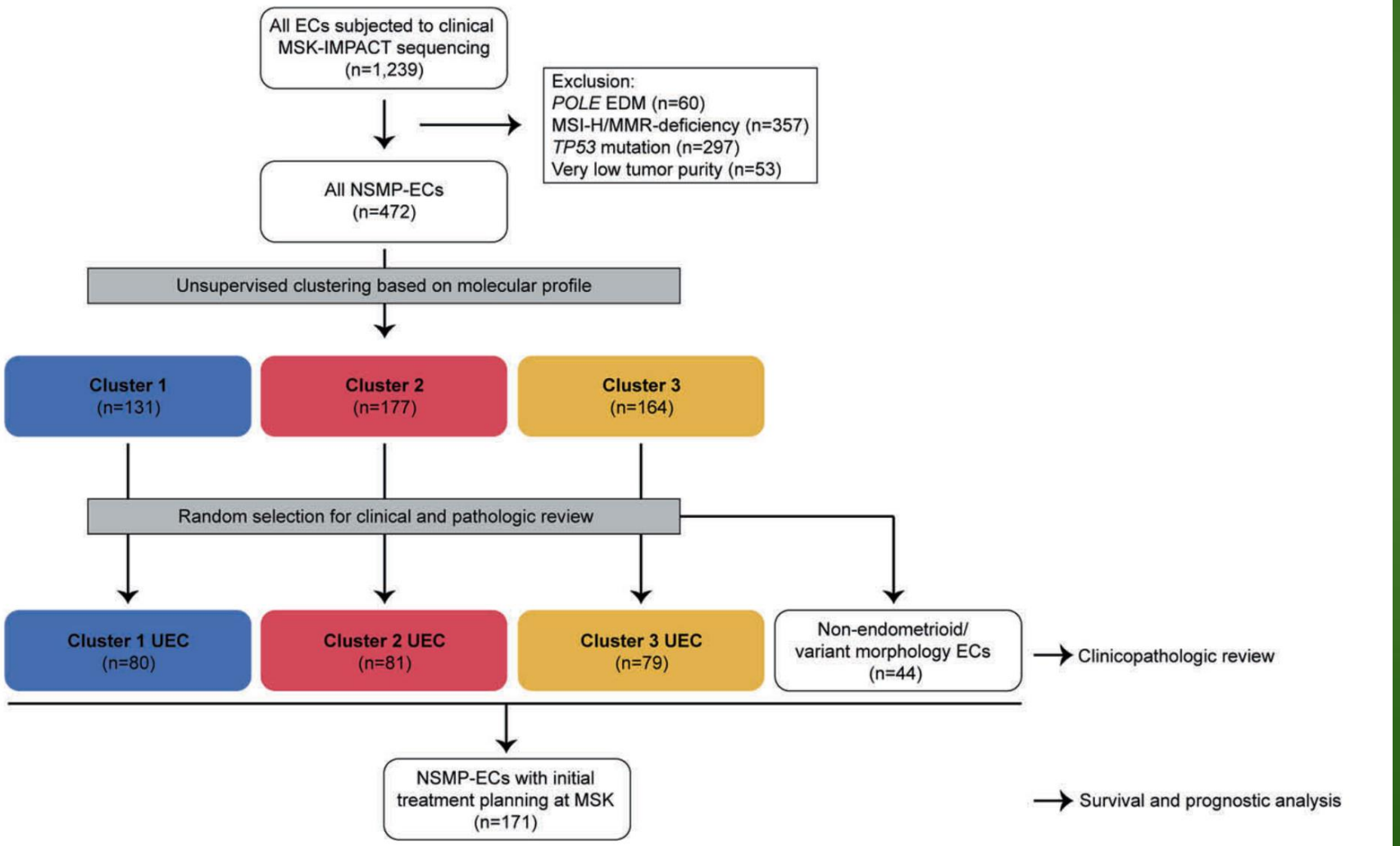
- Diagnosis by exclusion.
- Most common type of endometrial cancers among all 4 subgroups, and most commonly in our daily practice.
- Molecular heterogeneity, clinically, and histologically diverse. But current treatment is largely based on traditional clinicopathologic parameters.



Bosse T. et al. Am J Surg Pathol. 2018
Kommoss F. et al. Br J Cancer 2018
Depreeuw J. et al. Am J Surg Pathol. 2017
Stelloo E. et al. Clin Cancer Res. 2016

Genomic landscape of endometrial carcinomas of no specific molecular profile

Amir Momeni-Boroujeni[1], Bastien Nguyen[2,3], Chad M. Vanderbilt[1], Marc Ladanyi[1], Nadeem R. Abu-Rustum[4], Carol Aghajanian[5], Lora H. Ellenson[1], Britta Weigelt[1,6]✉ and Robert A. Soslow[1,6]✉



Momeni-Boroujeni A. et al. Mod Pathol 2022

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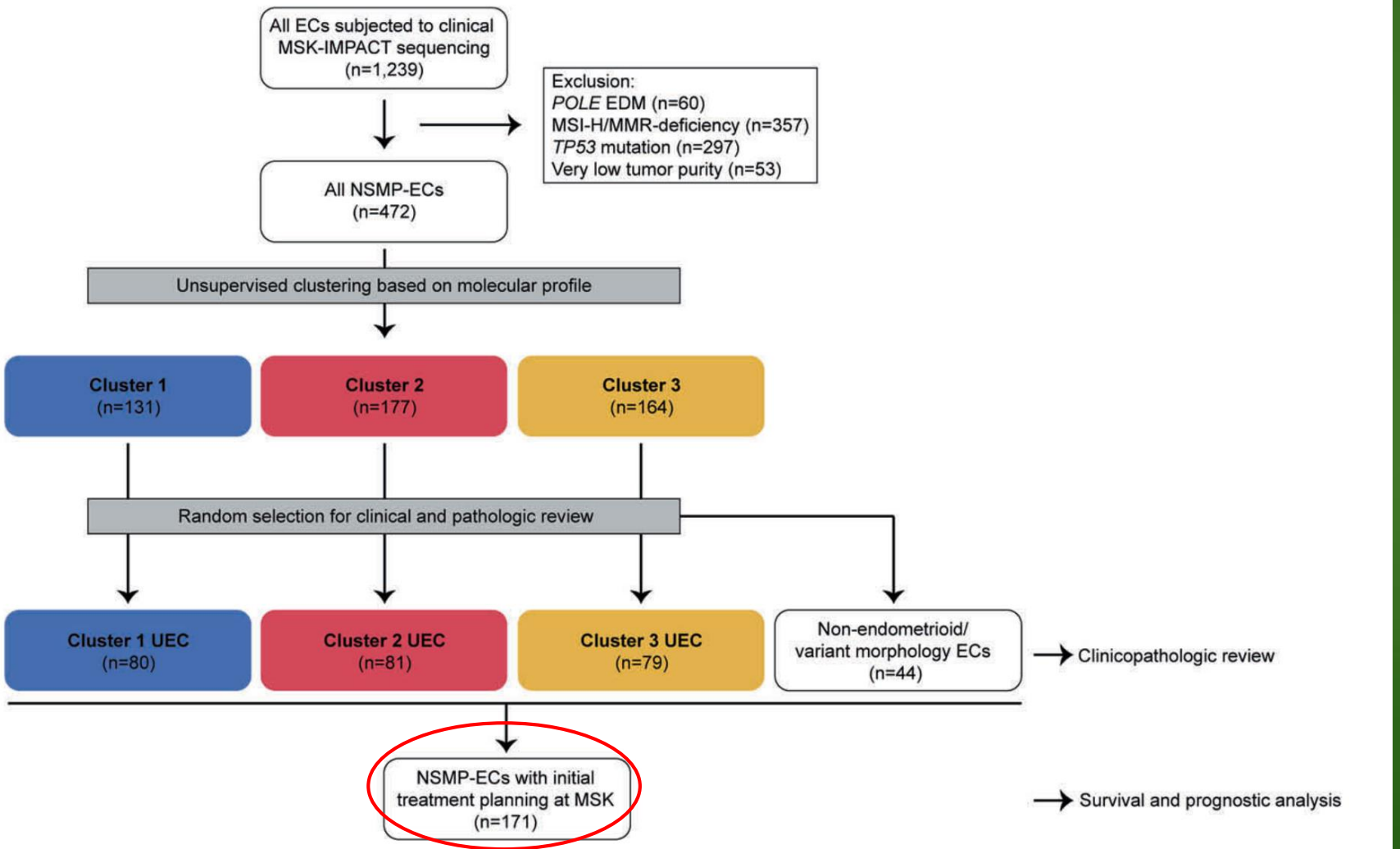
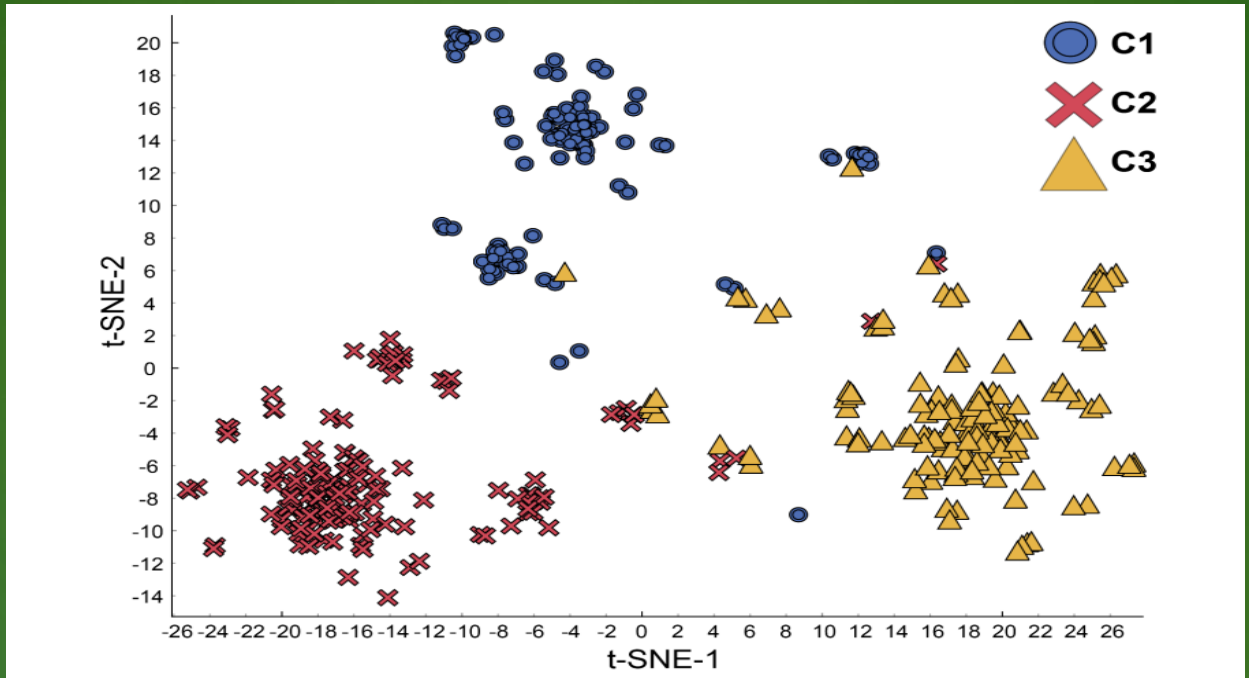


Momeni-Boroujeni A. et al. Mod Pathol 2022

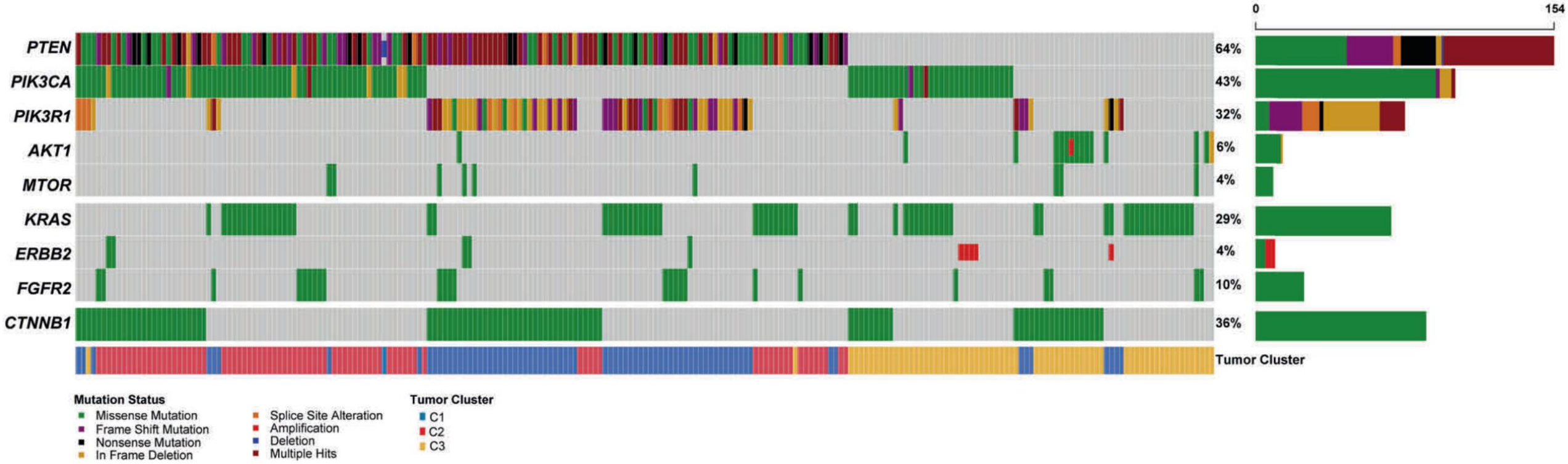
Endometrial Ca, NSMP: Endometrioid Ca



Supplementary Figure S1. Two-dimensional t-Distributed Stochastic Neighbor Embedding (t-SNE) map based on molecular features of endometrial carcinomas of no special molecular profile (NSMP-EC). HDBSCAN clustering shows the presence of 3 distinct molecular clusters among NSMP-EC tumors. C1, Cluster 1; C2, Cluster 2; C3, Cluster 3.

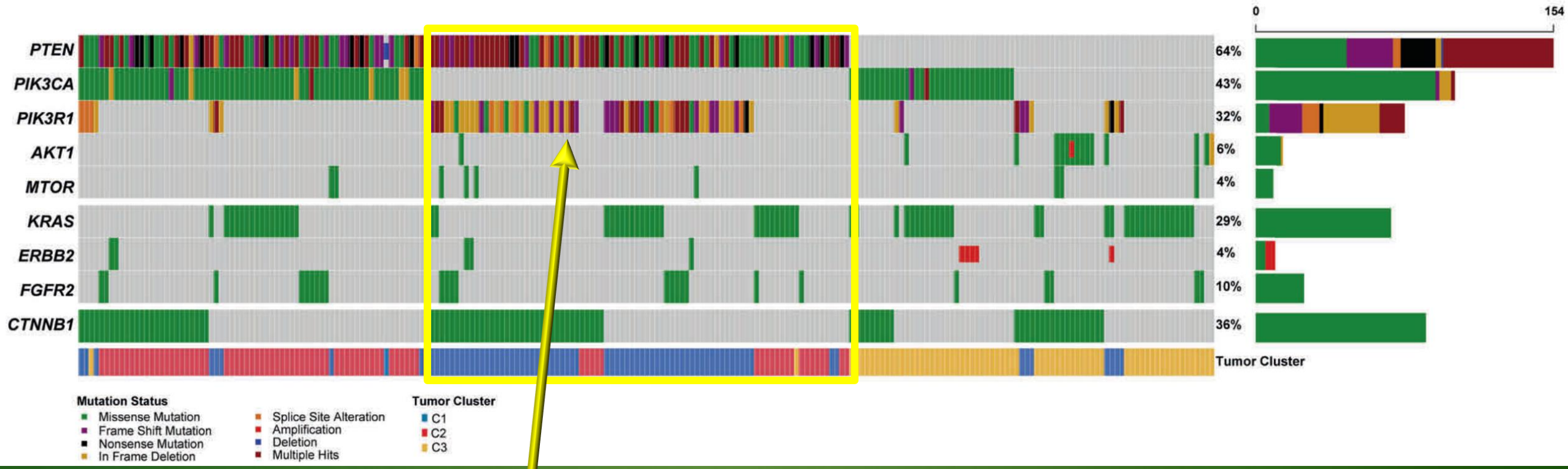
- Tumor mutational burden (median # somatic mutations) C1>C2>C3
- Fraction of gene alterations (chromosomal instability) C3>C1, C2
- CNA: Chromosome 1q gains: C3>C1>C2

Momeni-Boroujeni A. et al. Mod Pathol 2022



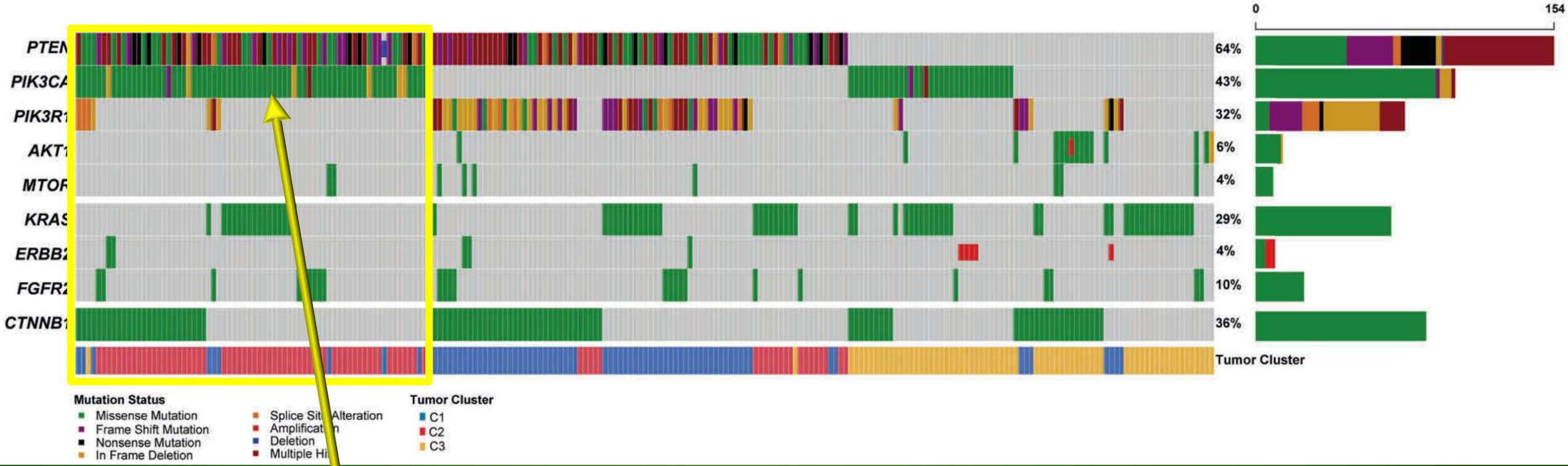
- Cluster 1
- Cluster 2
- Cluster 3

Momeni-Boroujeni A. et al. Mod Pathol 2022



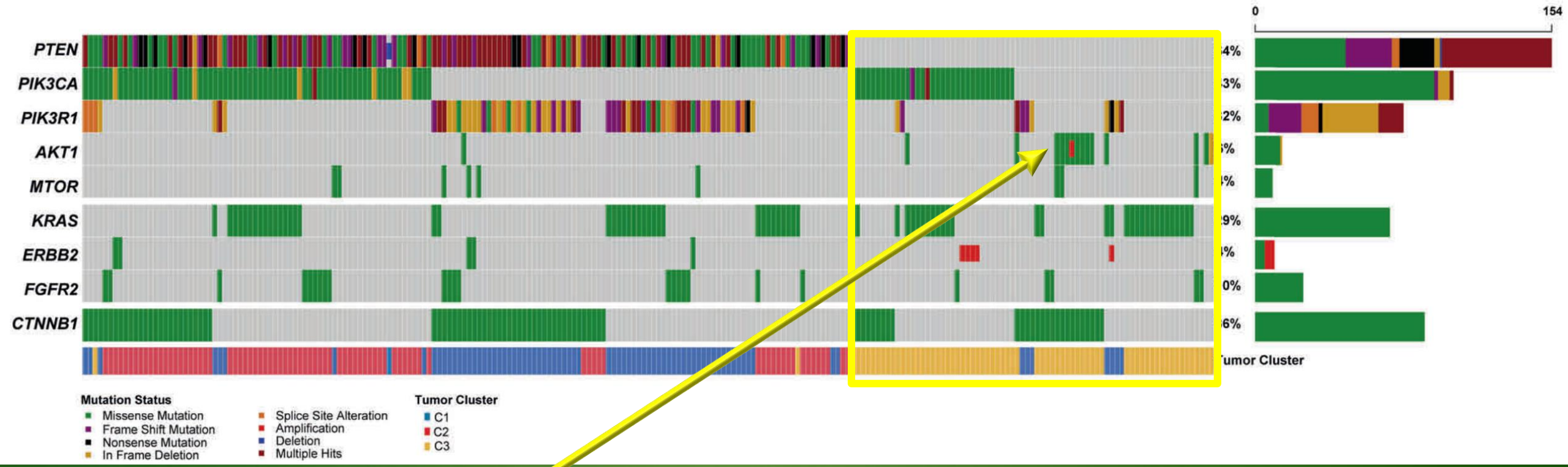
- Cluster 1 *PTEN* and *PIK3R1*
- Cluster 2
- Cluster 3

Momeni-Boroujeni A. et al. Mod Pathol 2022



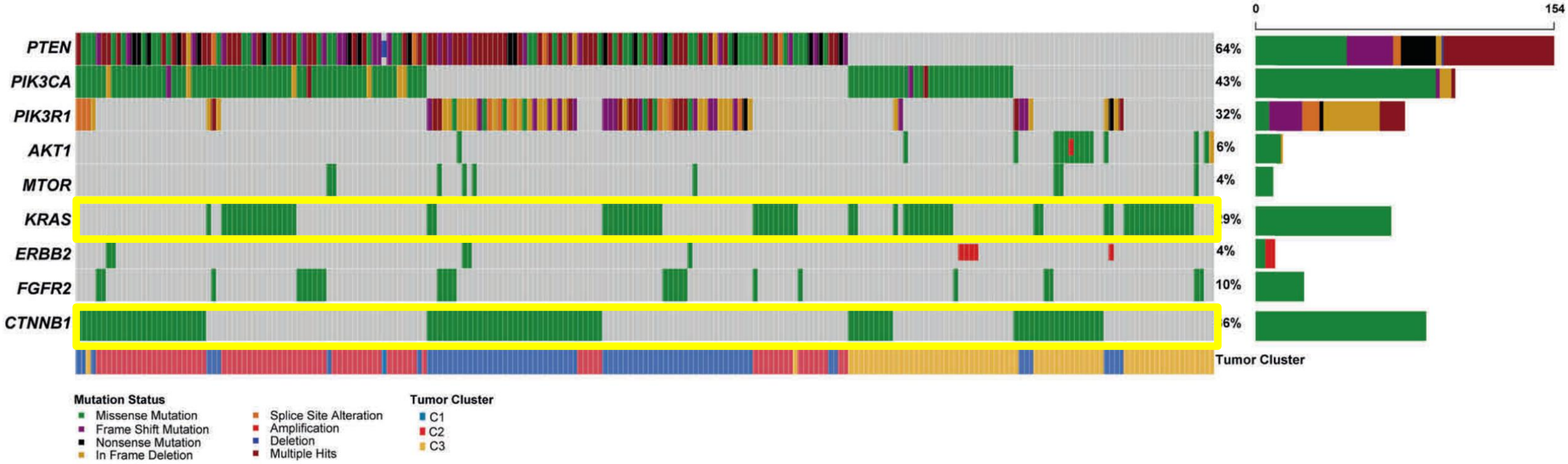
- Cluster 1 *PTEN* and *PIK3R1*
- Cluster 2 *PTEN* and *PIK3CA*
- Cluster 3

Momeni-Boroujeni A. et al. Mod Pathol 2022



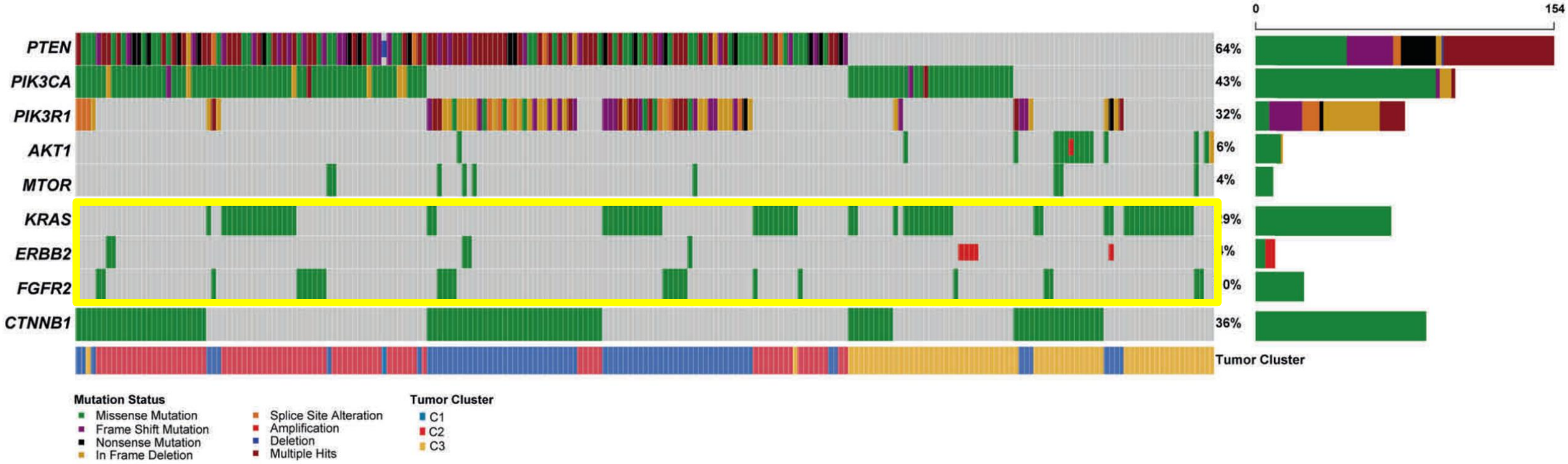
- Cluster 1 *PTEN* and *PIK3R1*
- Cluster 2 *PTEN* and *PIK3CA*
- Cluster 3 *AKT1 (hotspot E17K)*

Momeni-Boroujeni A. et al. Mod Pathol 2022



- *KRAS* and *CTNNB1* alterations are mutually exclusive.

Momeni-Boroujeni A. et al. Mod Pathol 2022

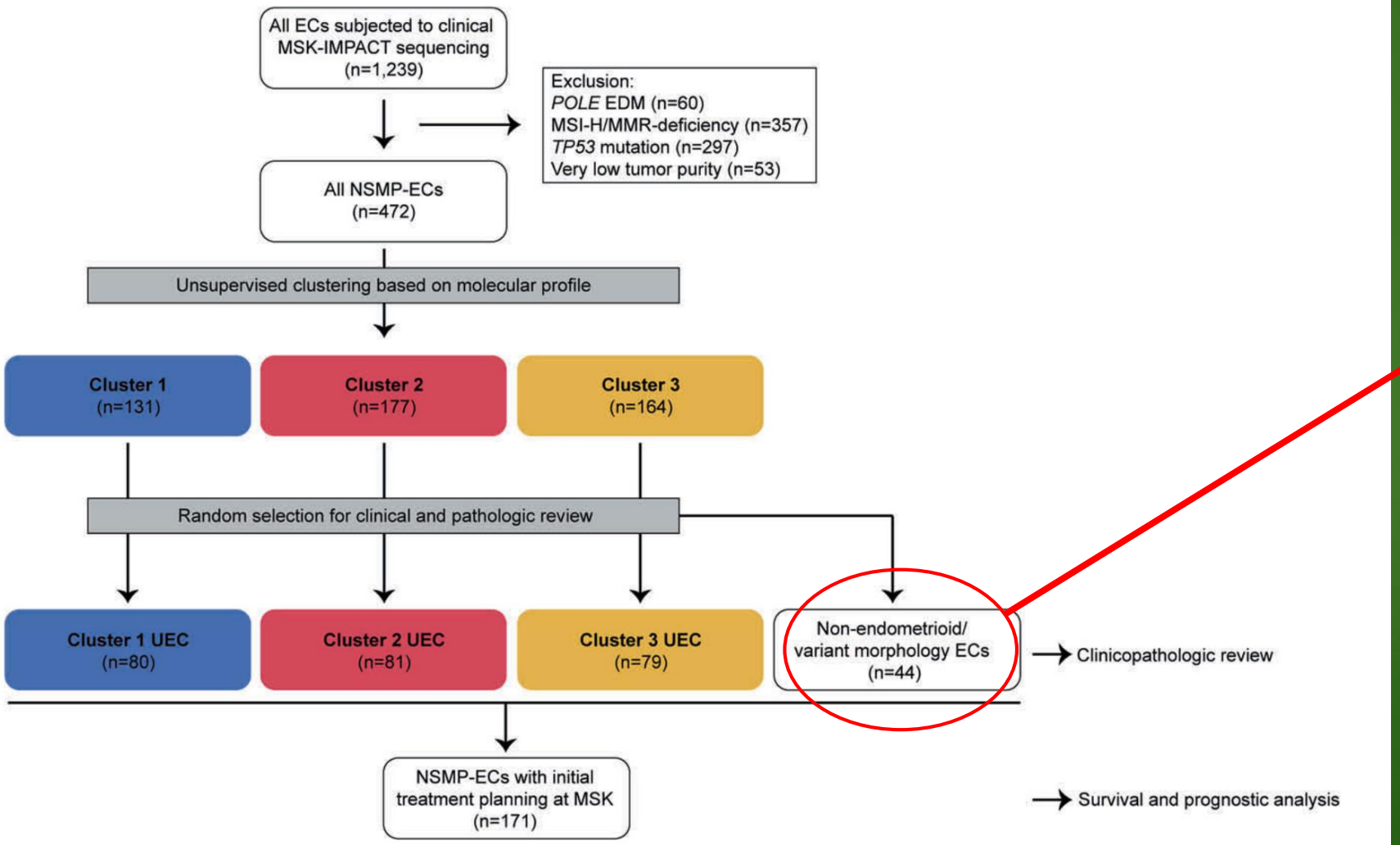


- *KRAS*, *ERBB2*, and *FGFR2* alterations are mutually exclusive.

Momeni-Boroujeni A. et al. Mod Pathol 2022

Genomic landscape of endometrial carcinomas of no specific molecular profile

Amir Momeni-Boroujeni[1], Bastien Nguyen[2,3], Chad M. Vanderbilt[1], Marc Ladanyi[1], Nadeem R. Abu-Rustum[4], Carol Aghajanian[5], Lora H. Ellenson[1], Britta Weigelt[1,6]✉ and Robert A. Soslow[1,6]✉



Non-endometrioid:

- Clear cell
- Mesonephric-like
- CS
- Serous

Endometrioid-variants:

- EC, ambiguous
- CHEC

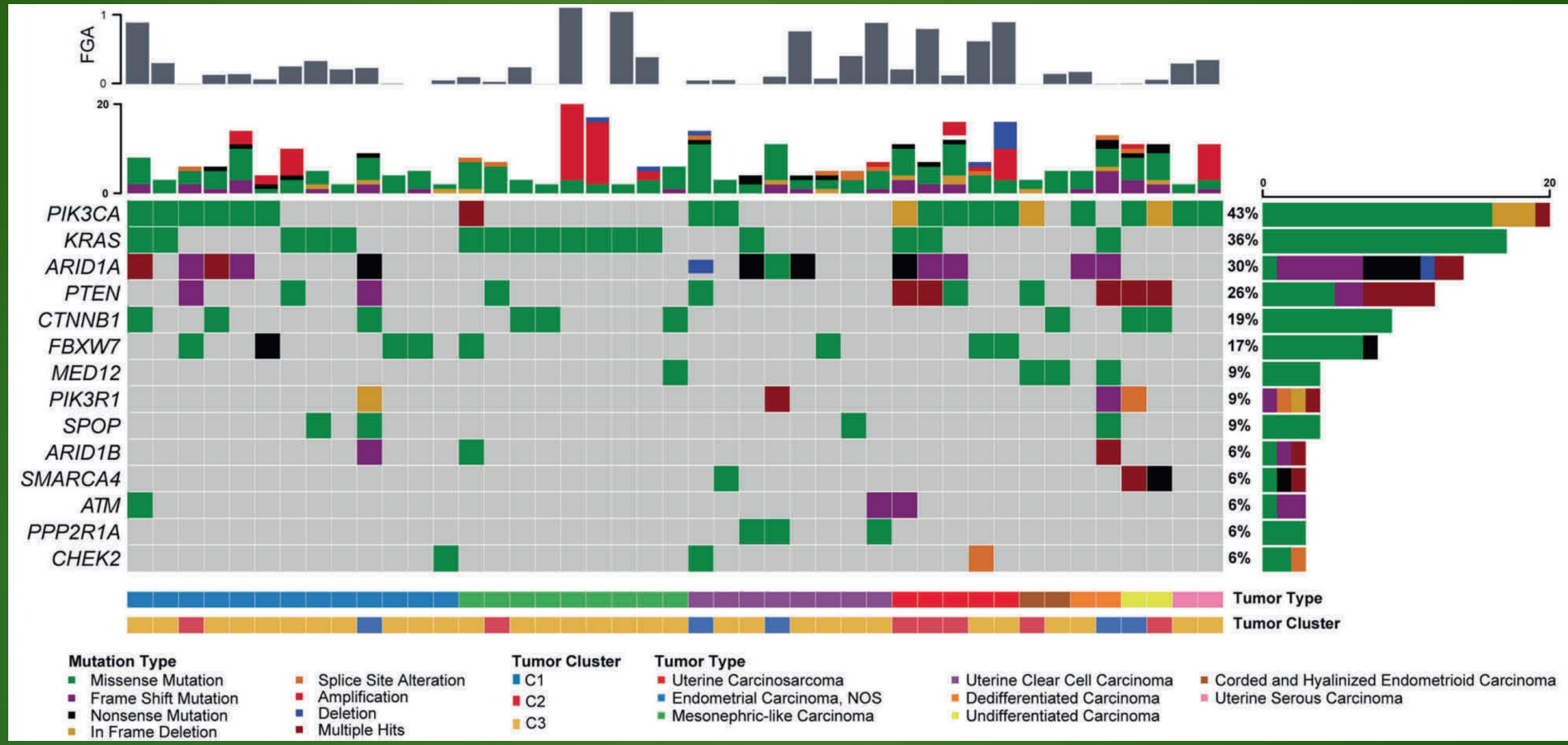
Momeni-Boroujeni A. et al. Mod Pathol 2022

Endometrial Ca, NSMP: Non-Endometrioid, variant endometrioid Ca

- 44 cases:
- High-grade endometrioid Ca with ambiguous morphology (9.7%)
- Clear cell Ca (4.9%)
- Mesonephric-like Ca (2.5%)
- Carcinosarcoma (1.9%)
- Uterine serous Ca (1.3%)
- Corded and hyalinized endometrioid Ca (0.8%)
- Dedifferentiated Ca (0.6%)
- Undifferentiated Ca (0.4%)

Momeni-Boroujeni A. et al. Mod Pathol 2022

Endometrial Ca, NSMP: Non-Endometrioid, variant endometrioid Ca



- 72.7% (n =32) clustered into C3; 15.9% (n=7) clustered into C2; 11.4% (n=5) clustered into C1.
- Cluster 3 *PIK3CA*, *KRAS* single hit mutations

Momeni-Boroujeni A. et al. Mod Pathol 2022

Endometrial Ca, NSMP

- Three distinct molecular clusters

- C1 and C2:

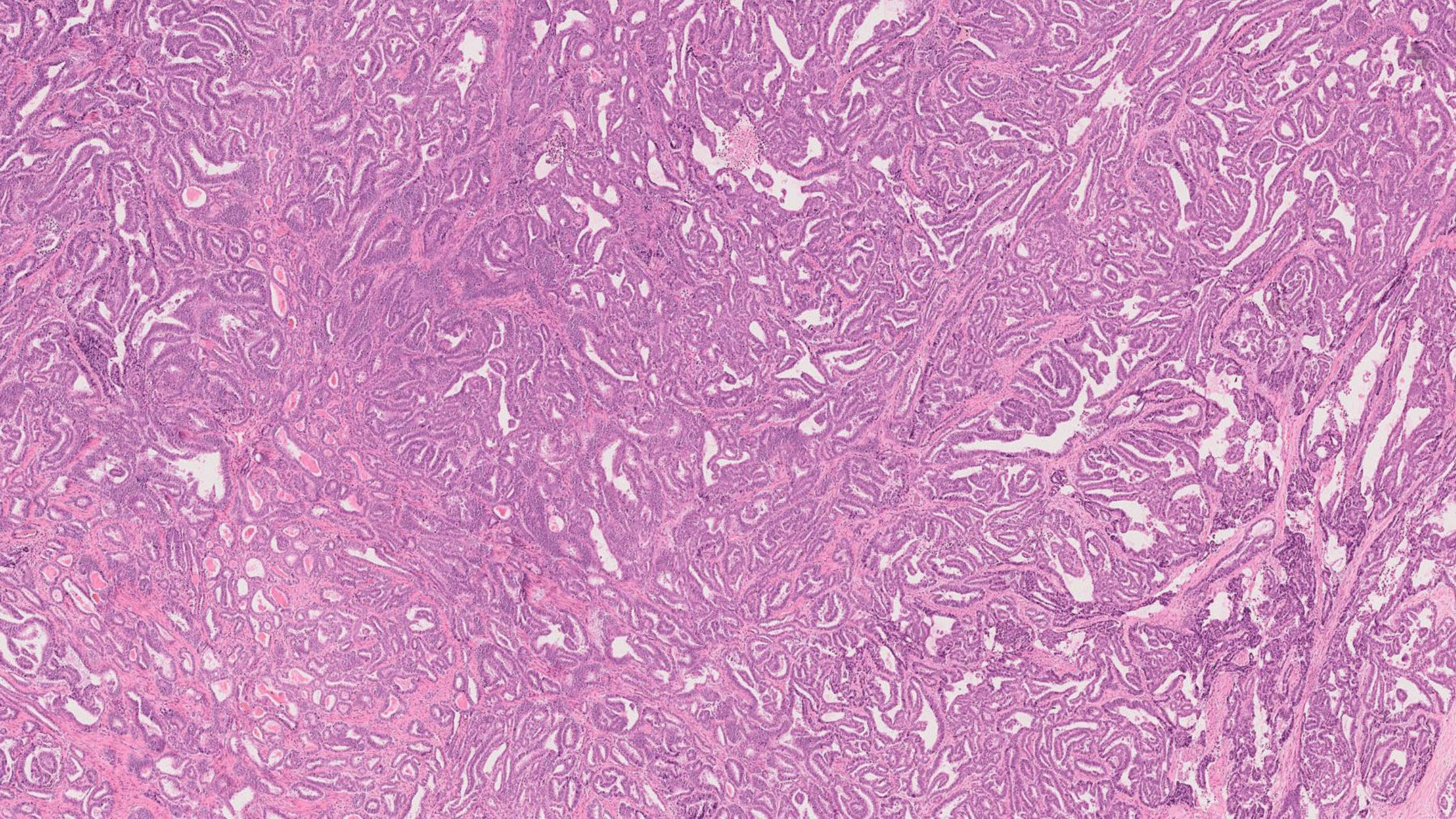
  Driven by activating mutations of PI3K pathway, *PTEN* mutations followed by truncating alterations of PIK3R1 (in C1) or PIK3CA (in C2).

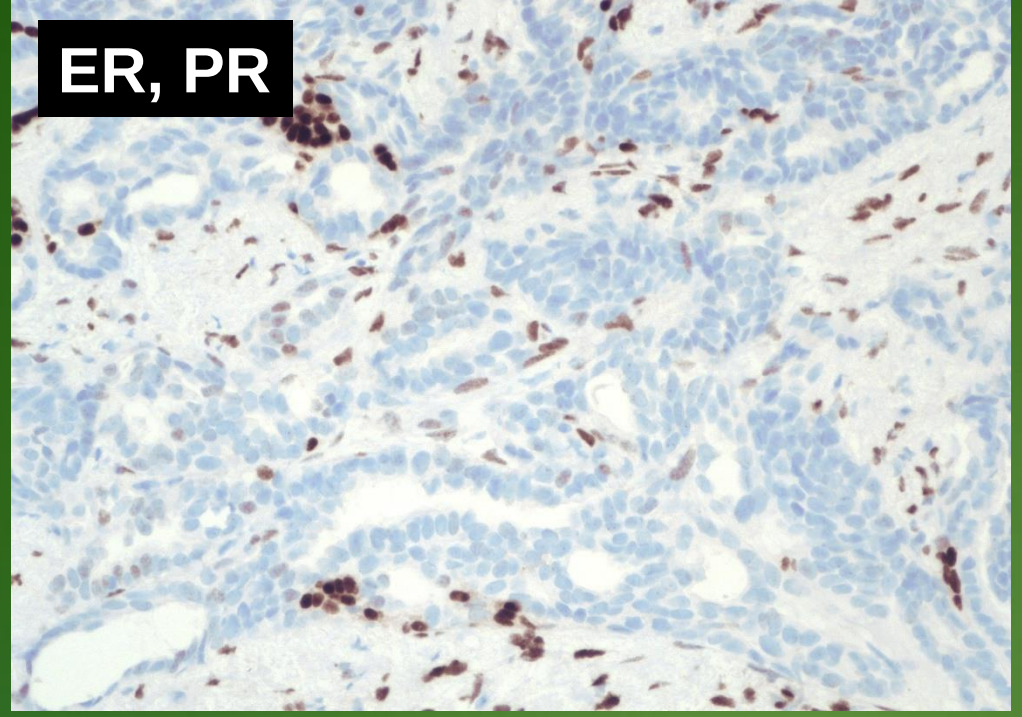
- C3:

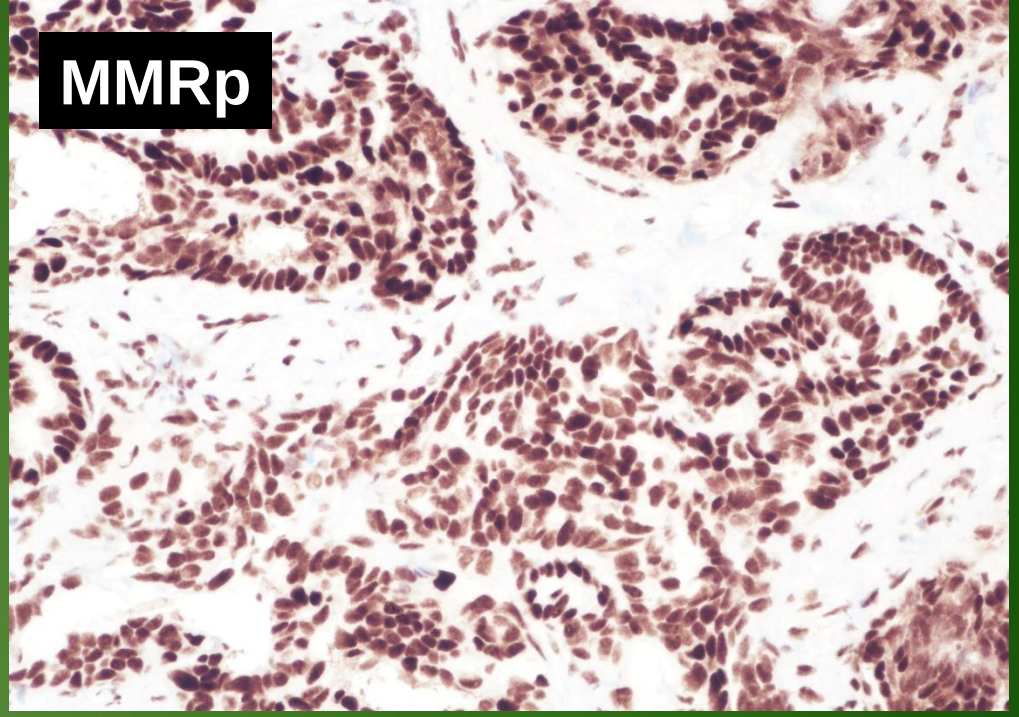
  Single hits in *PIK3CA*, *AKT1*, *KRAS*.

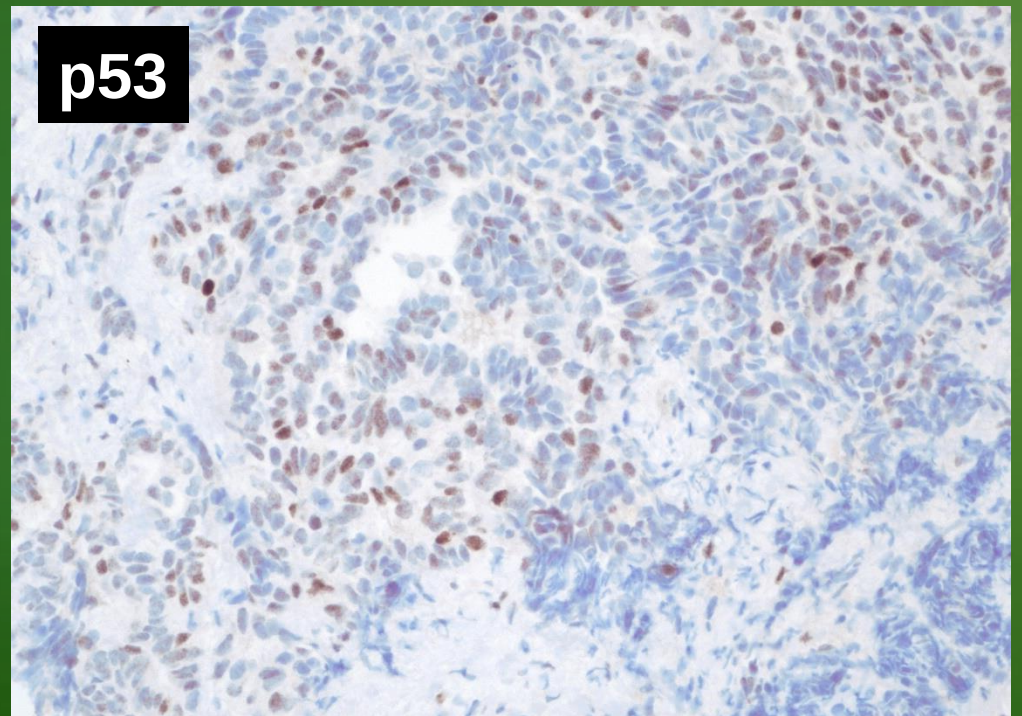
  FIGO 3, ER/PR –ve/weak, stage III/IV, LVSI.

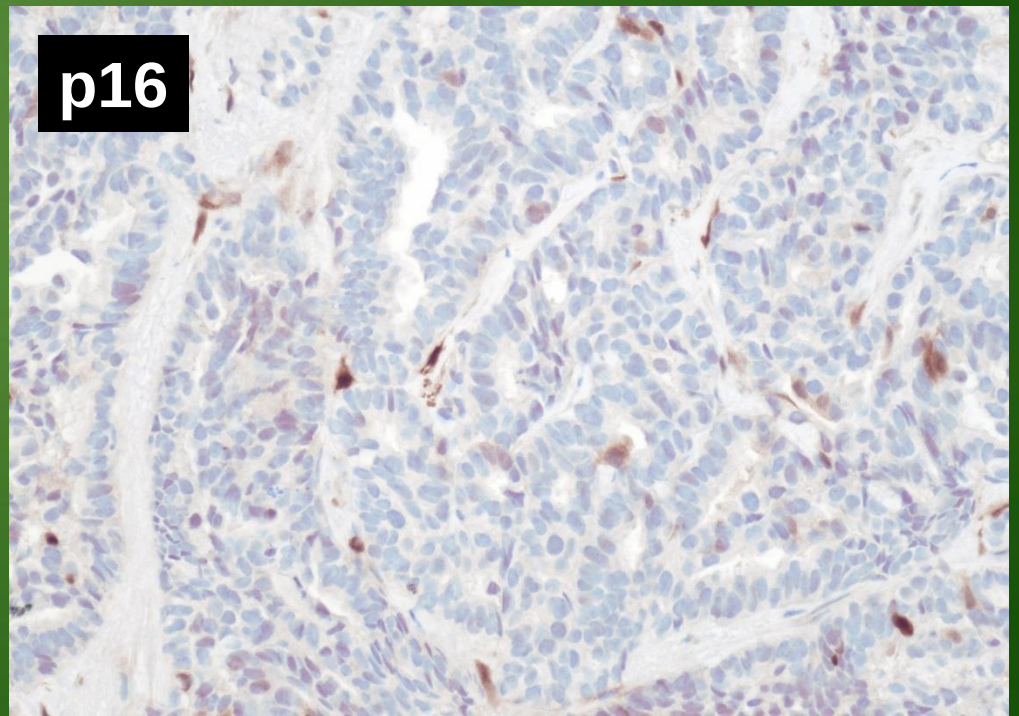
Momeni-Boroujeni A. et al. Mod Pathol 2022

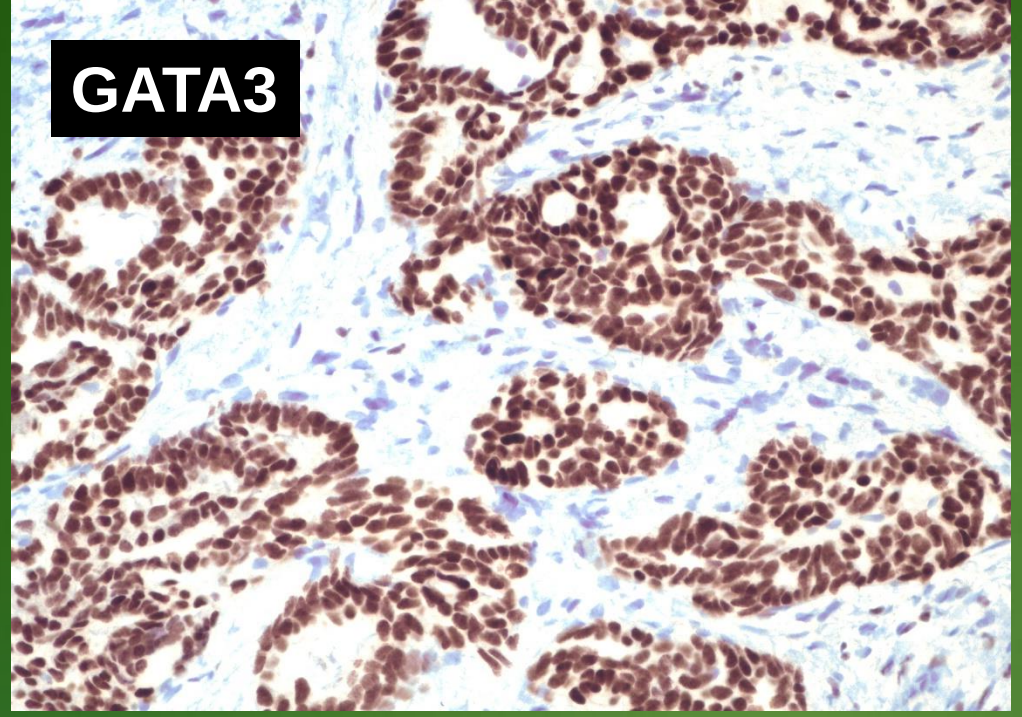


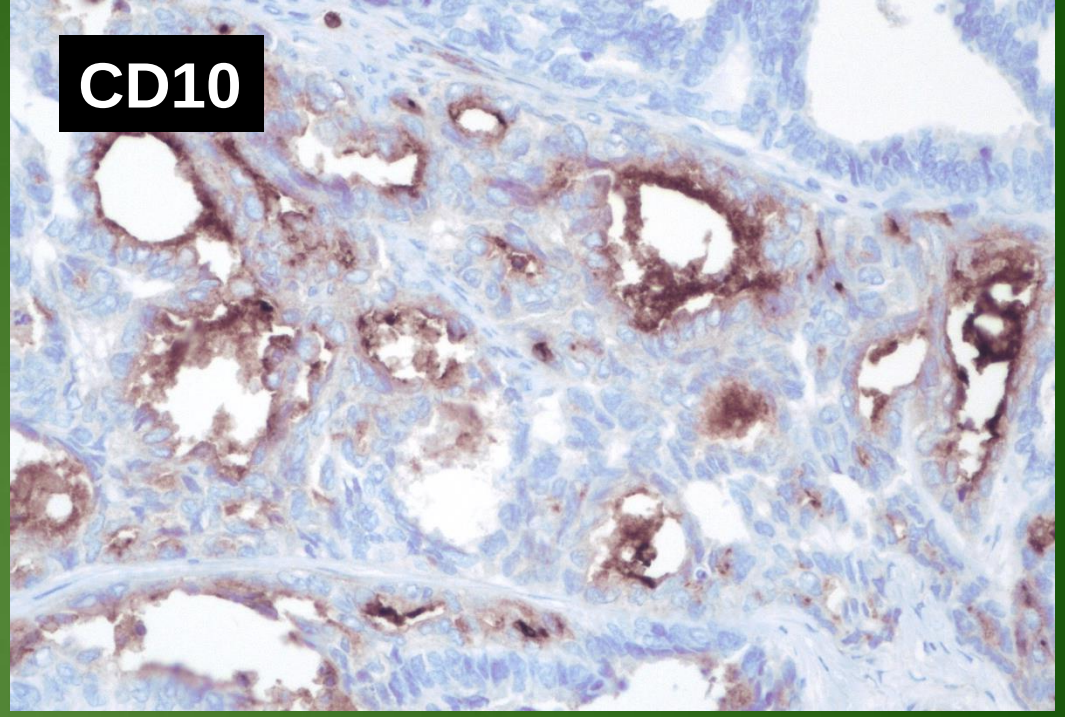

ER, PR

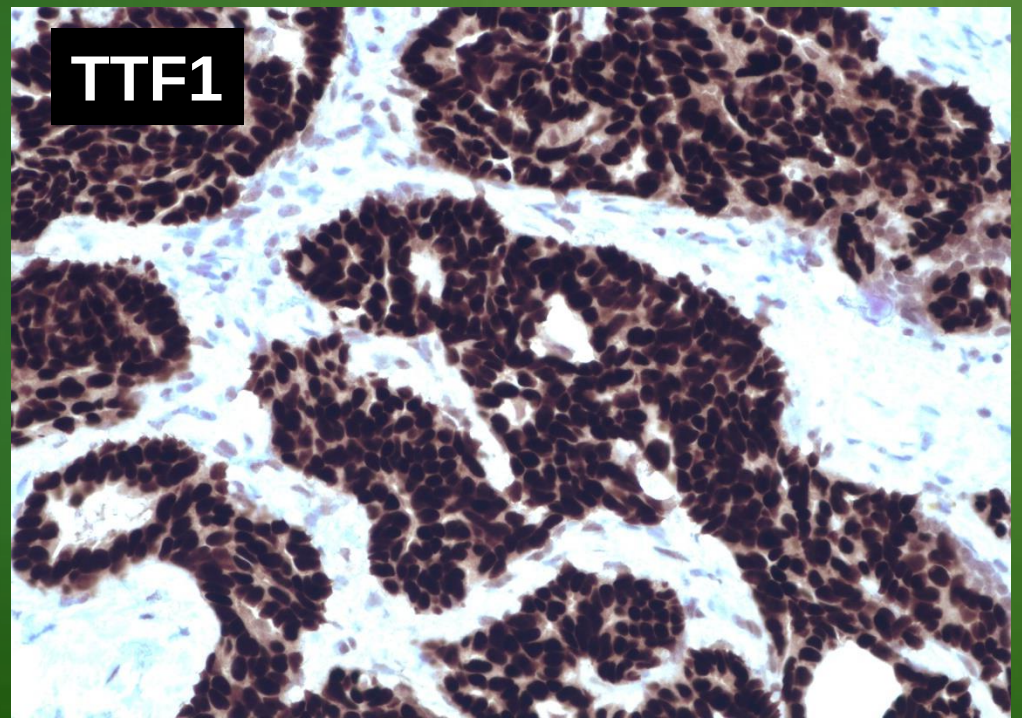

MMRp

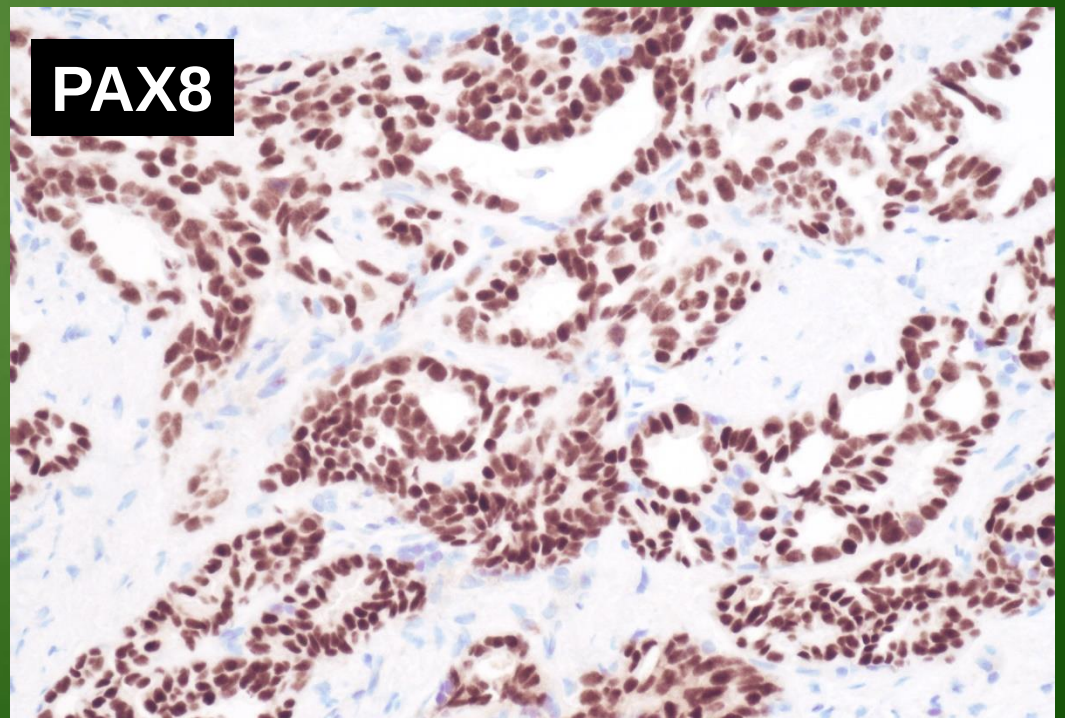

p53


p16


GATA3


CD10


TTF1

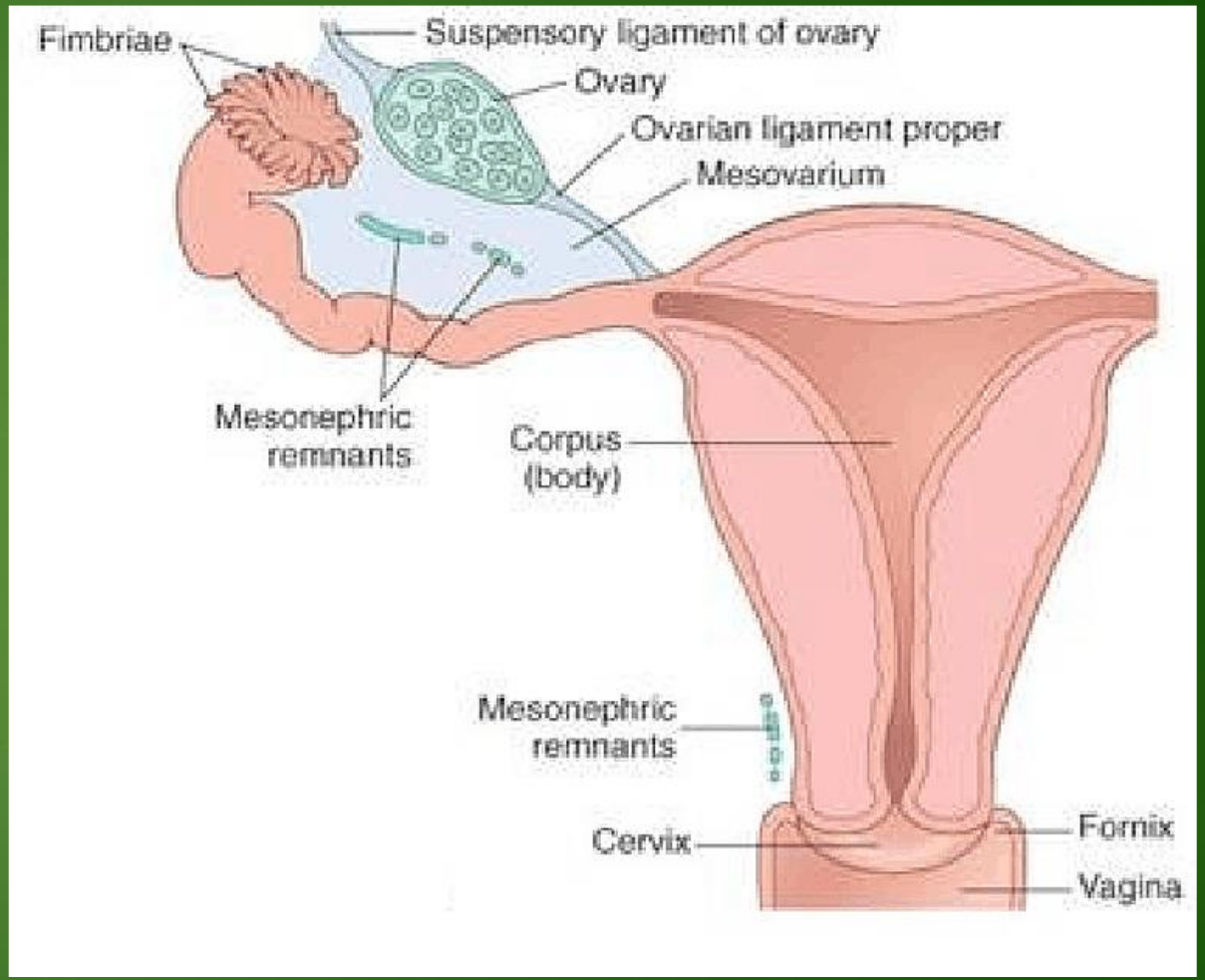

PAX8

Mesonephric Carcinoma

Universidade do Estado do Rio de Janeiro

- Tumors developed from mesonephric remnants, mainly in the cervix, and are called **Mesonephric carcinomas.**

- Tumors with similar pathological features that developed in the endometrium and ovaries, were termed **‘Mesonephric-like carcinoma’.**



McFarland M. et al. Histopathology. 2016
Clement PB. Am J Surg Pathol. 1995
Wolfe SA. et al. Am J Obstet Gynecol. 1940
Schiller W. et al. Am J Cancer. 1939

Mesonephric-like Carcinoma: Pathogenesis

- Mesonephric-like carcinomas (endometrium and ovaries) share similar **morphologic and immunohistochemical profile** with cervical mesonephric carcinomas. But the genomic profiles are not identical.

- Lack of associated mesonephric remnants or mesonephric hyperplasia.

- Mullerian origin, with transdifferentiation.

Mirkovic J. et al. Histopathology. 2023
Da Silva. et al. Mod Pathol. 2021
Na K. Am J Surg Pathol. 2019
McCluggage WG. et al. Histopathology. 2018
Mirkovic J. et al. Am J Surg Pathol. 2018
Chapel DB. et al. Int J Gynecol Pathol. 2017
McFarland M. et al. Histopathology. 2016

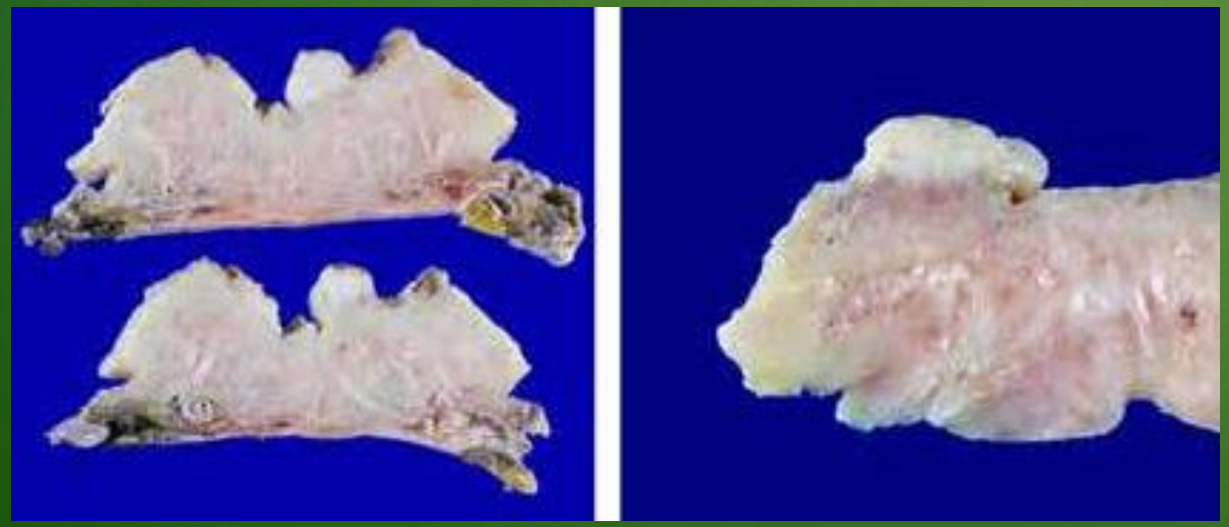
Mesonephric-like Carcinoma: Pathogenesis

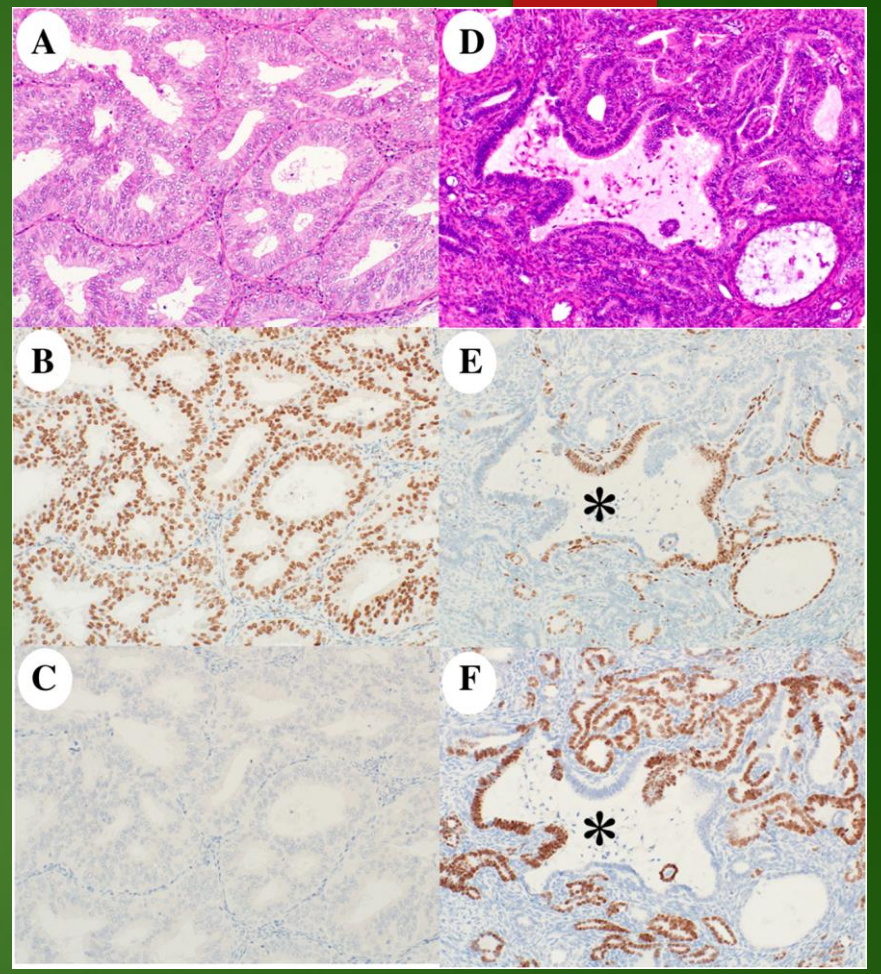
- A Mullerian origin is supported by identical genetic alterations in both components:
- In the ovaries:
  - **Serous borderline tumor**-mesonephric-like Ca (n=2)
  - **Low-grade serous carcinoma**-mesonephric-like Ca (n=1)
  - **Mucinous borderline tumors**-mesonephric-like Ca (n=2)
  - **Serous borderline/low-grade serous carcinoma-**mesonephric-like Ca (n=3)
  - Others, coexisting endometriosis, or adenofibroma.

Da Silva. et al. Mod Pathol. 2021
McCluggage WG. et al. Histopathology 2020
Dundr P. et al. Diagn Pathol. 2020
Chapel DB. et al. Int J Gynecol Pathol. 2018

Mesonephric-like Carcinoma: Pathogenesis

- In uterine corpus a Mullerian origin is also supported by:
- Anatomically, in the **endometrium**, not myometrium.
- Components of classical endometrioid carcinoma, atypical hyperplasia, carcinosarcoma.

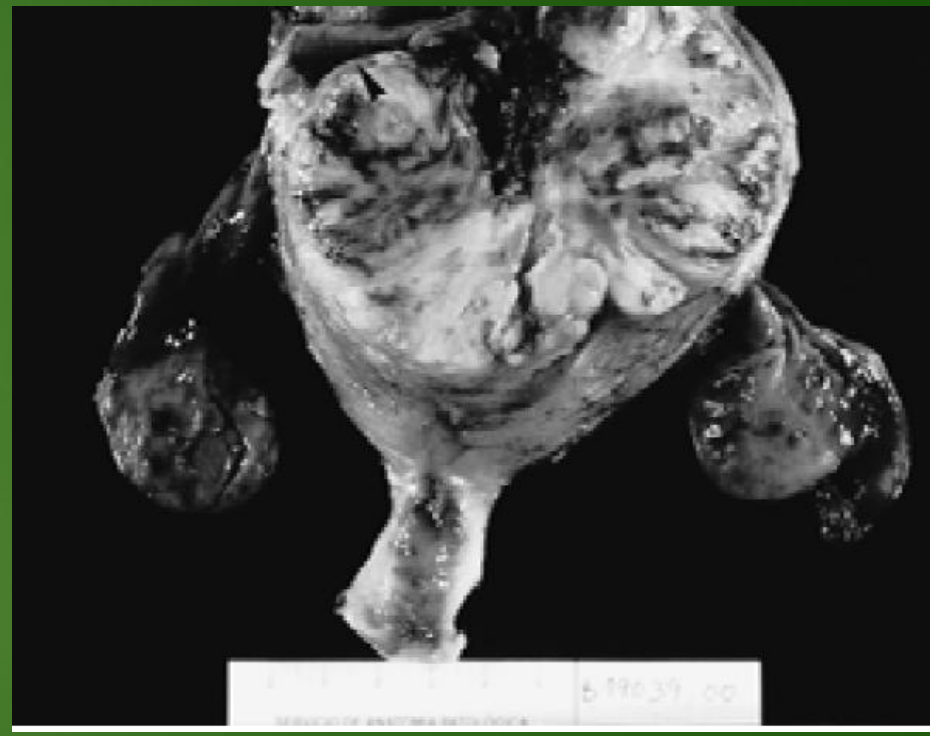




Mirkovic J. et al. Histopathology. 2023
Pors J. et al. Am J Surg Pathol. 2021
Deolet E. et al. J Clin Med. 2021
Na K. et al. Am J Surg Pathol 2019
Yano M. et al. Diagn Pathol 2019
McCluggage WG. et al. Histopathology 2018
McFarland M. et al. Histopathology 2016

Mesonephric-like Carcinoma of Endometrium: Clinical and Pathological Features

- TRUE mesonephric carcinoma is supported by an exclusive myometrial location without endometrial involvement.
- To-date, 118 cases reported.
- Rare (<1%, 4/570) of all endometrial carcinomas (Kolin et al. from BWH, Boston).

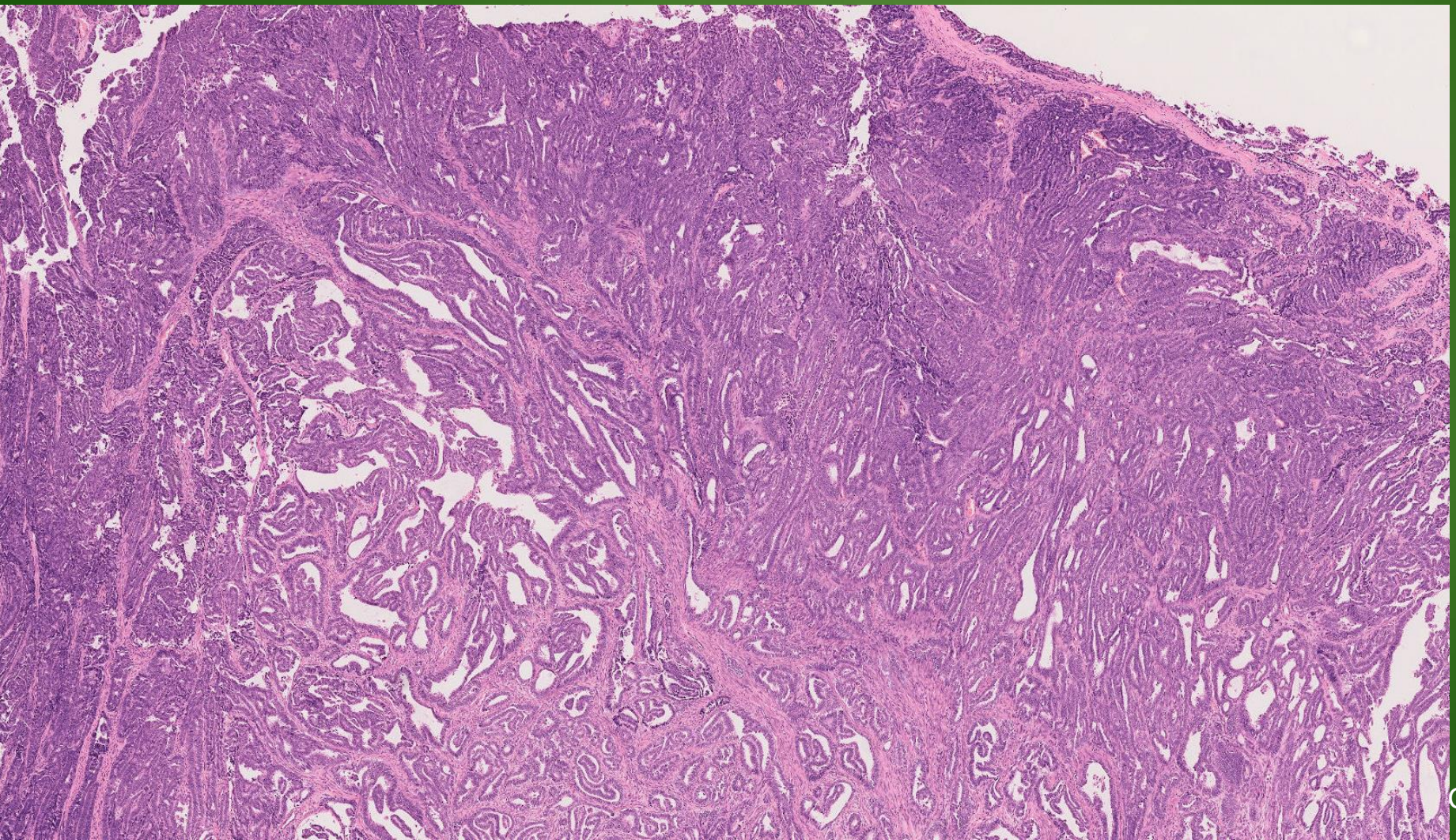


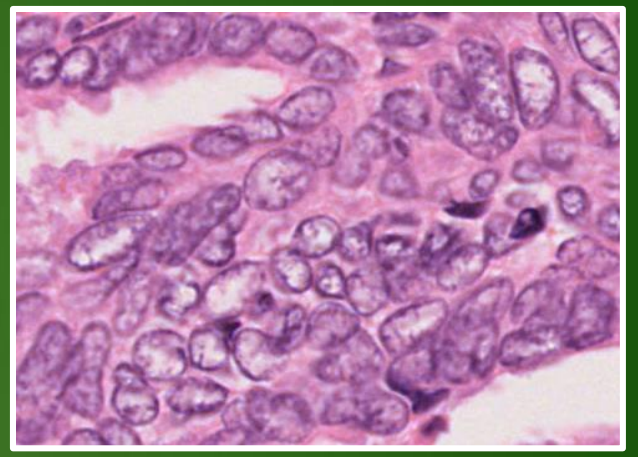
- **Vaginal bleeding**
- Median age of patients = **61** years
- Mean size of tumors = **5.1** cm

Deolet E. et al. J Clin Med. 2021
Horn LC. et al. J Cancer Res and Clin Oncol. 2020
Kolin DL. et al. Am J Surg Pathol. 2019
Zheng L. et a. Int J Gynecol Pathol. 2018
Ando H. et al. Diagn Pathol. 2017
Ordi J. et al. Am J Surg Pathol. 2001

Mesonephric-like Carcinoma of Endometrium: Architecture

- Ductal (glandular, villoglandular)

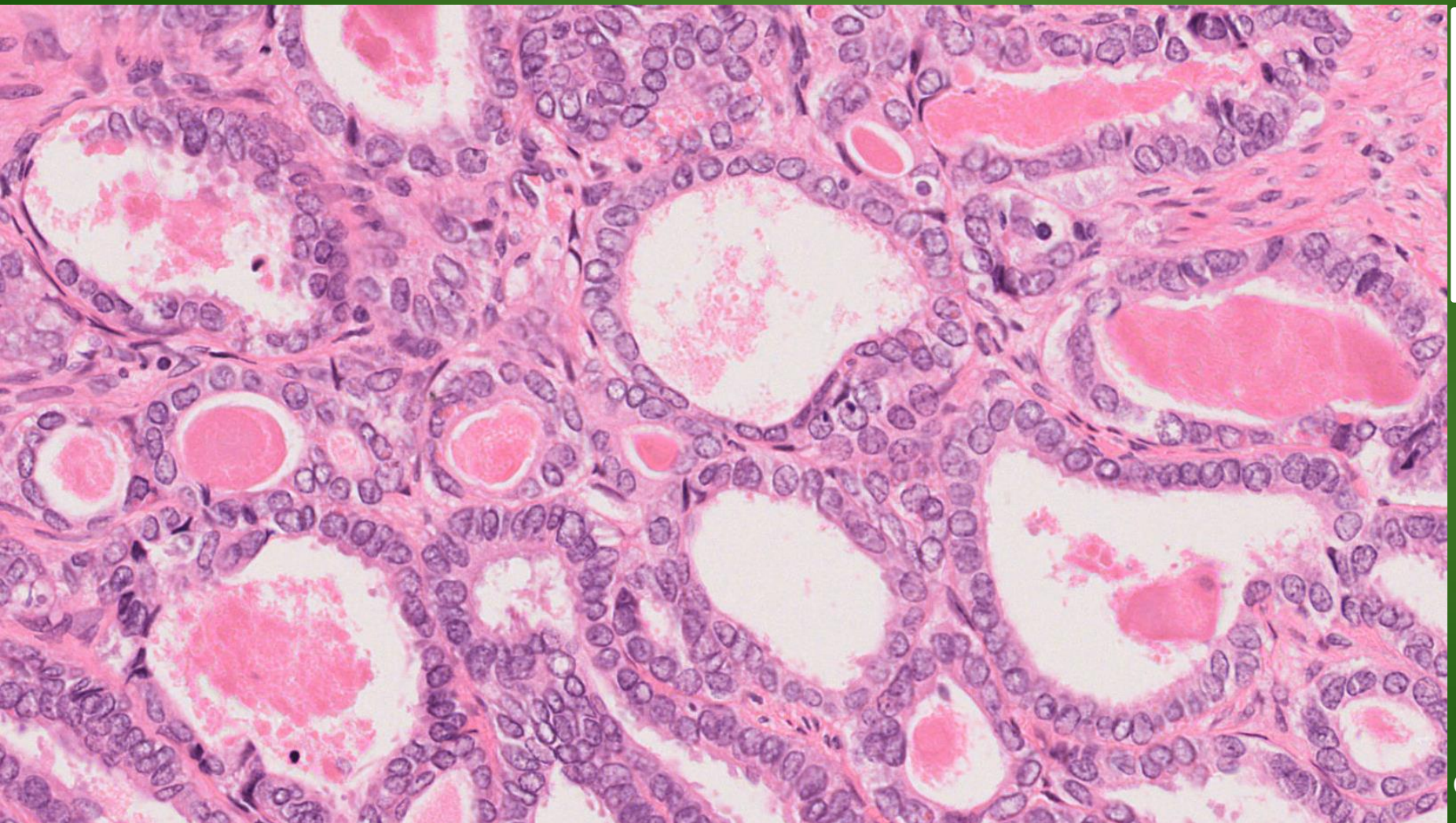


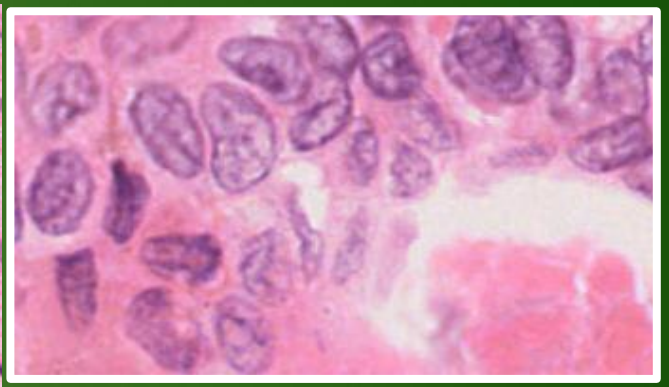


Pors J. et al. Am J Surg Pathol. 2018
McFarland M. et al. Histopathology. 2016
Clement PB. et al. Am J Surg Pathol. 1995

Mesonephric-like Carcinoma of Endometrium: Architecture

- Small tubular (eosinophilic colloid-like secretion)

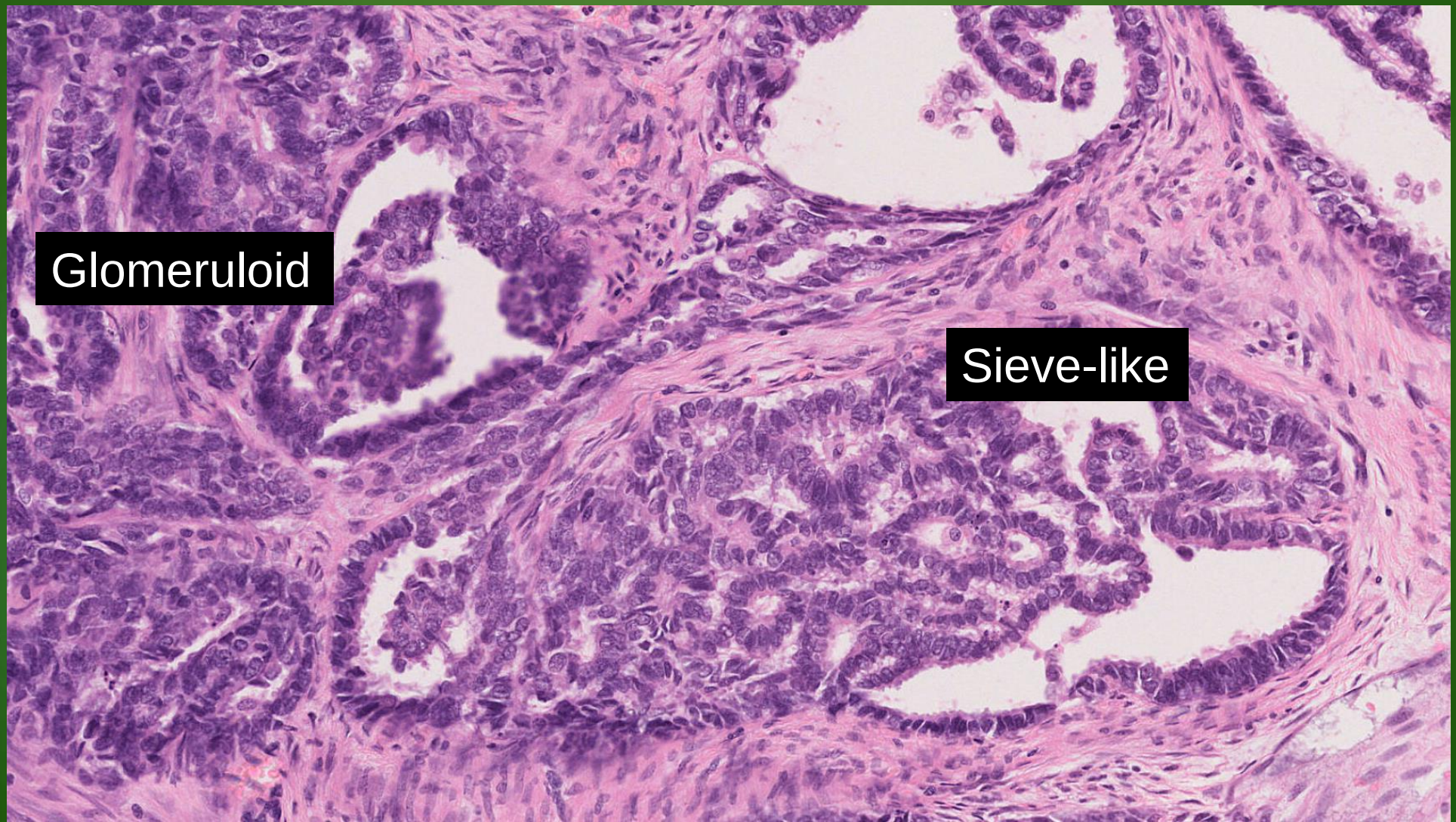




Da Silva EM. et al. Mod Pathol 2021
Euscher E. et al. Am J Surg Pathol 2020
McFarland M. et al. Histopathology 2016
Clement PB. et al. Am J Surg Pathol 1995

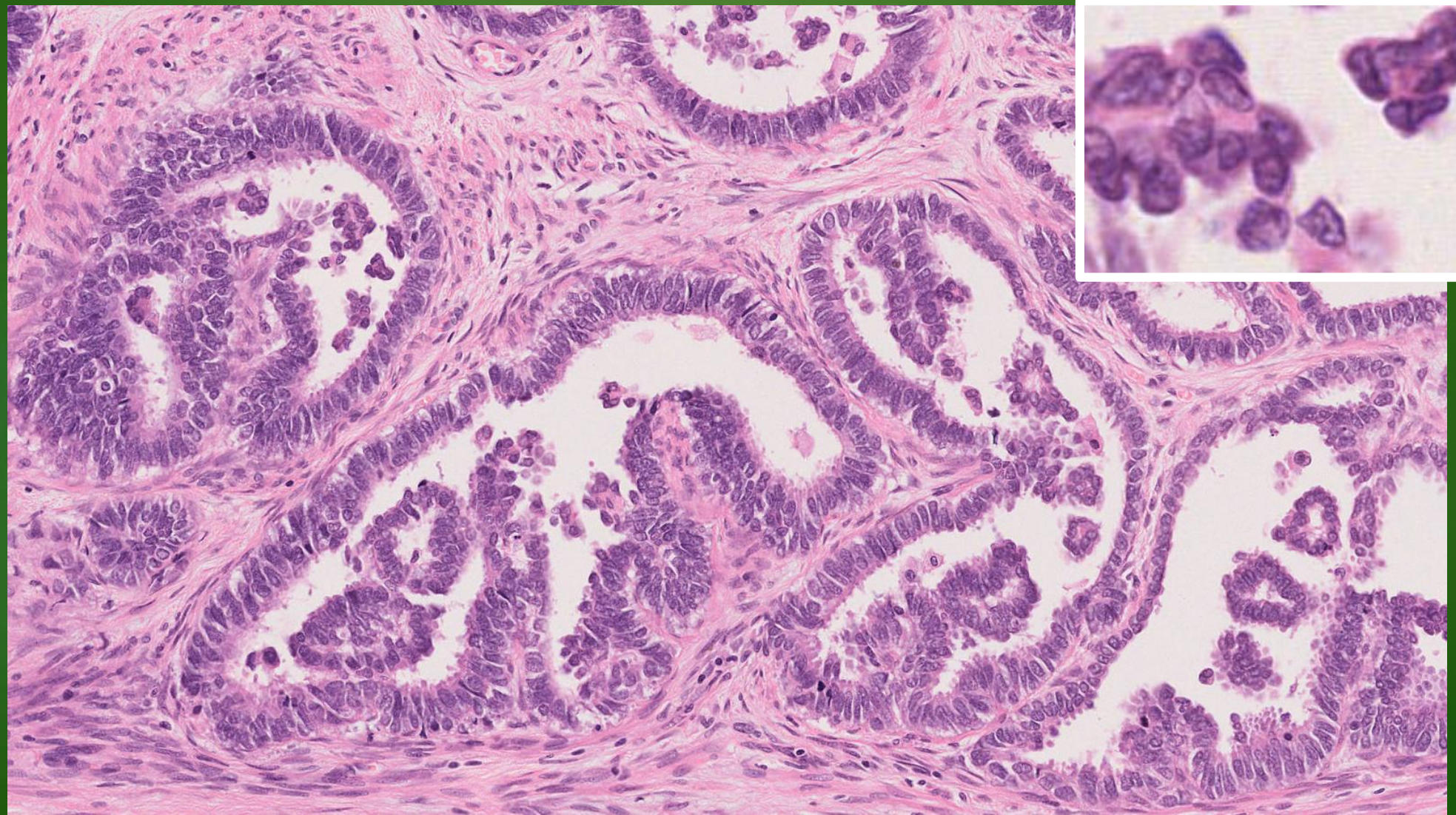
Mesonephric-like Carcinoma of Endometrium: Architecture

- Sieve-like, Glomeruloid



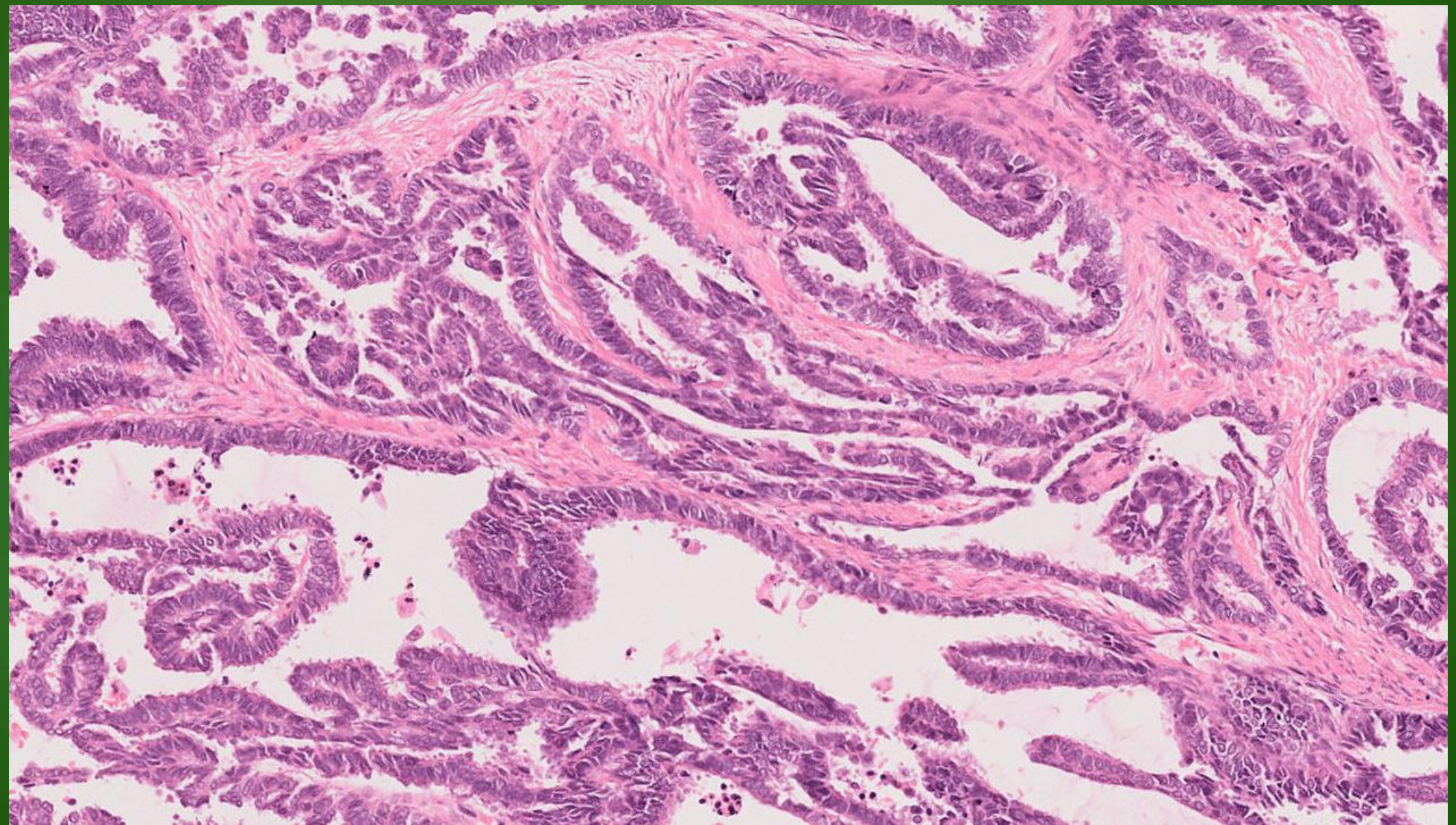
Mesonephric-like Carcinoma of Endometrium: Architecture

- Micropapillary



Mesonephric-like Carcinoma of Endometrium: Architecture

- Retiform



Targeted Genomic Profiling Reveals Recurrent *KRAS* Mutations in Mesonephric-like Adenocarcinomas of the Female Genital Tract

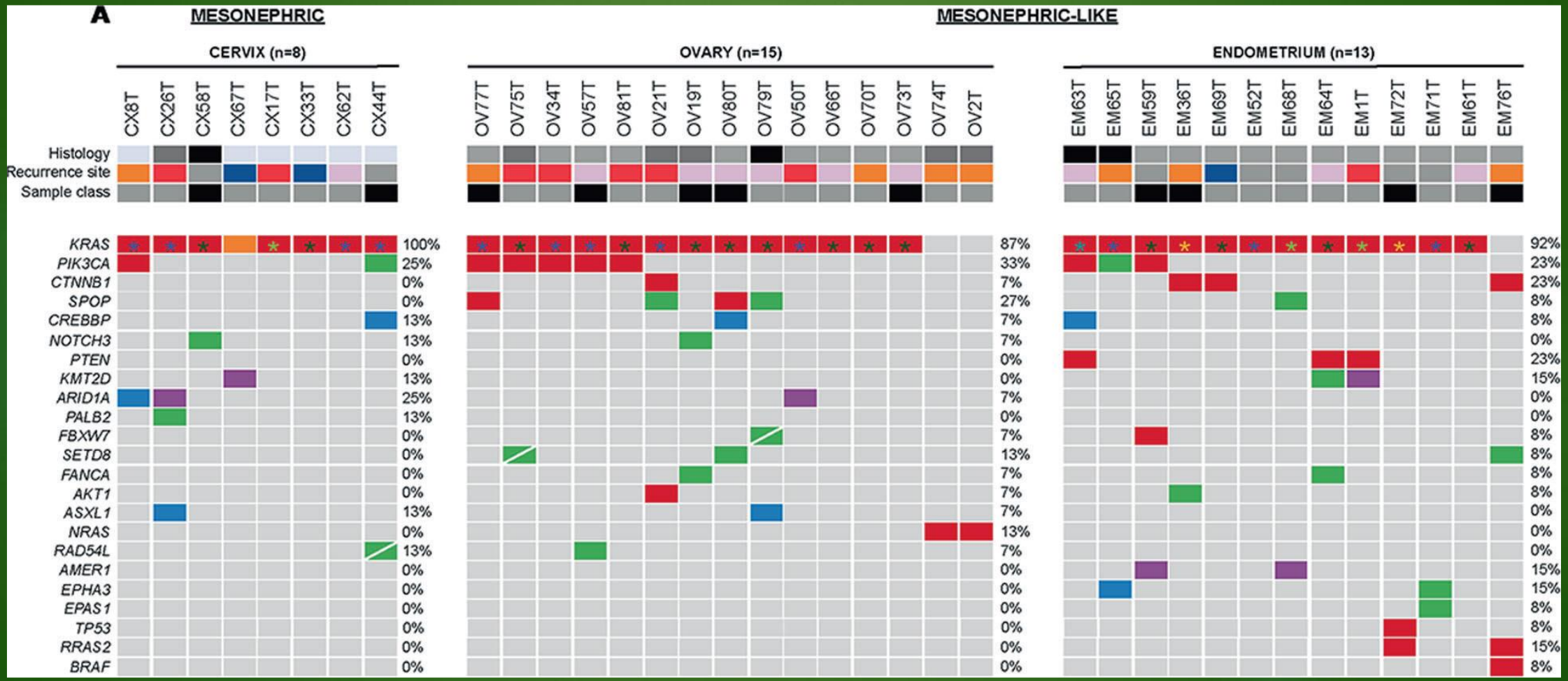
Jelena Mirkovic, MD, PhD, Marie McFarland, FRCPath,† Elizabeth Garcia, PhD,‡ Lynette M. Sholl, MD,‡ Neal Lindeman, MD,‡ Laura MacConaill, PhD,‡§ Fei Dong,‡ Michelle Hirsch, MD, PhD,‖ Marisa R. Nucci, MD,‖ Charles M. Quick, MD,¶ Christopher P. Crum, MD,‖ W. Glenn McCluggage, FRCPath,† and Brooke E. Howitt, MD‖*

		Ovarian tumors				Uterine tumors		
		#1	#2	#3	#4	#5	#6	#7
Common SNVs	*KRAS*	p.G12D	p.G12D	p.G12D	p.G12D	p.G12V	p.G12V	p.G12V
	PIK3CA		p.F909L p.R88Q p.M1004I		p.N345I	p.E542K		
Common CNVs	1 q gain							
	1 p loss							
	Ch10 gain							
	Chr12 gain							

Mirkovic J. et al. Mod Pathol 2018

Mesonephric and mesonephric-like carcinomas of the female genital tract: molecular characterization including cases with mixed histology and matched metastases

Edaise M. da Silva[1] · Daniel J. Fix[1,2] · Ana Paula Martins Sebastiao[1,3] · Pier Selenica[1] · Lorenzo Ferrando[1,4] · Sarah H. Kim[5] · Anthe Stylianou[5] · Arnaud Da Cruz Paula[5] · Fresia Pareja[1] · Evan S. Smith[5] · Ahmet Zehir[1] · Jason A. Konner[6] · Karen Cadoo[6] · Jorge S. Reis-Filho[1] · Nadeem R. Abu-Rustum[5] · Jennifer J. Mueller[5] · Britta Weigelt[1] · Kay J. Park[1]



Da Silva EM. et al. Mod Pathol. 2021

Mesonephric-like Carcinoma of Endometrium: NSMP Profile

- ***KRAS* hotspot mutations**, or *NRAS/BRAF* (mutually exclusive).
- *AMER1*, *EPHA3*, and *RRAS2* alterations (endometrial mesonephric-like Ca) .
- *PTEN, CTNNB1, PIK3CA, SPOP, FBXW7*, and *FANCA* alterations (Mullerian).
- CNA: Gains involved chromosome **1q**, 10p, 12, and 20 (Chr 10 gains associated with metastasis in 2 studies).

Da Silva EM. et al. Mod Pathol. 2021
Euscher ED. et al. Res Clin Oncol 2020
Na K. et al. Am J Surg Pathol. 2019
Mirkovic J. et al. Am J Surg Pathol. 2018
Mirkovic J. et al. Mod Pathol. 2015

Clinicopathologic and Molecular Characteristics of Mesonephric Adenocarcinoma Arising From the Uterine Body

Kiyong Na, MD, PhD and Hyun-Soo Kim, MD, PhD

- Single institutional study (n=11).
- Clinicopathologic and molecular analysis.
- 6/11 (54.5%) developed metastasis (5 to lungs).
- On multivariate analysis, prognostic factors predicted metastasis: FIGO stage III/IV, mitotic count >10/10 HPFs, lymphovascular space invasion.
- Median PFS 7 months (range 4 - 10).

Na K. et al. Am J Surg Pathol 2020

Mesonephric-like Carcinoma of the Endometrium

A Subset of Endometrial Carcinoma With an Aggressive Behavior

Elizabeth D. Euscher, MD, Roland Bassett,† Dzifa Y. Duose, PhD,* Chieh Lan,* Ignacio Wistuba, MD,* Lois Ramondetta, MD,‡ Preetha Ramalingam, MD,* and Anais Malpica, MD**

- Single institutional study (n=23).
- Clinicopatholgic and molecular analysis.
- 48% at FIGO stage III/IV.
- On multivariate analysis, prognostic factors associated with poor survival were **mesonephric histology**, age, and stage, lymphovascular space invasion.
- Grading was not applicable (most tumors were grade 2).

Euscher ED. et al. Am J Surg Pathol 2020

Mesonephric-like Carcinoma of the Endometrium

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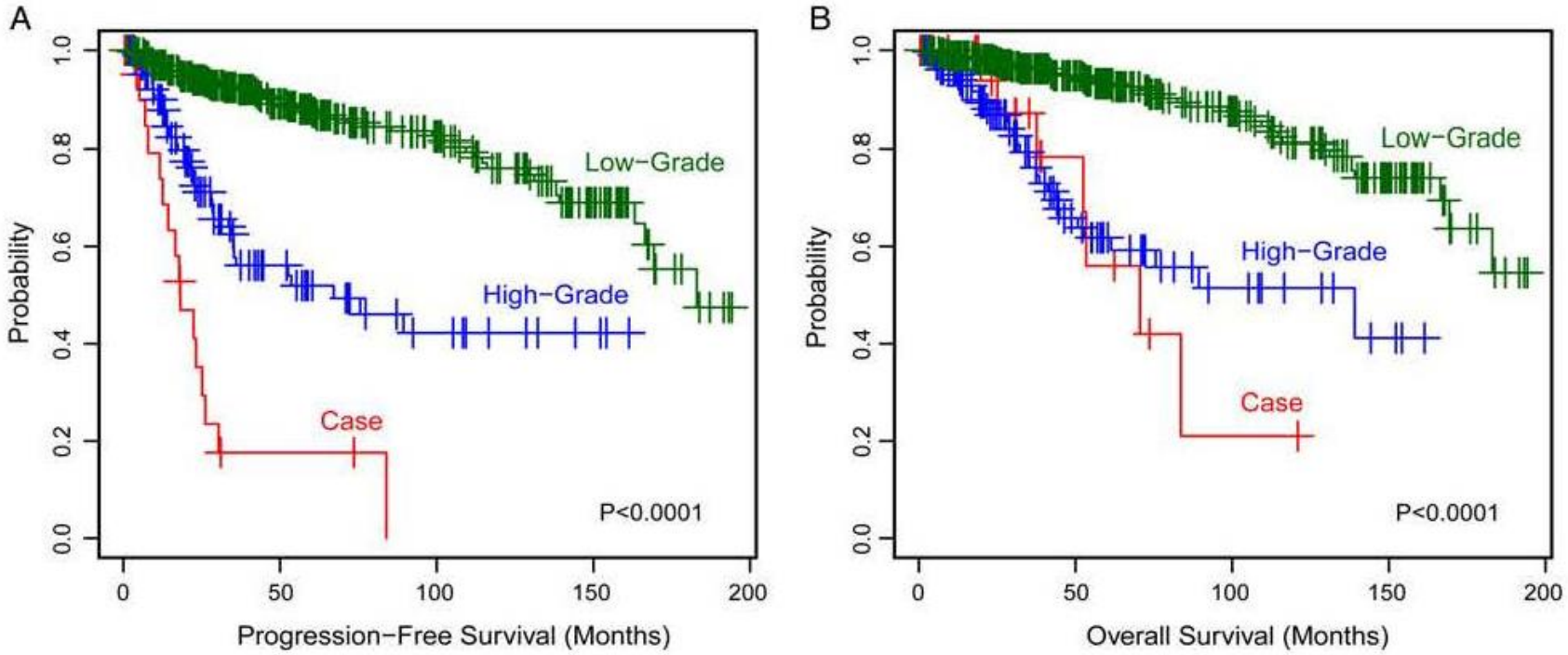


FIGURE 5. Kaplan-Meier plots of progression-free survival (A) and overall survival (B) by the group.

Median PFS (months) = ~18 MLCa, ~67 high-grade Ca (serous),183 low-grade Ca

Euscher ED. et al. Am J Surg Pathol 2020

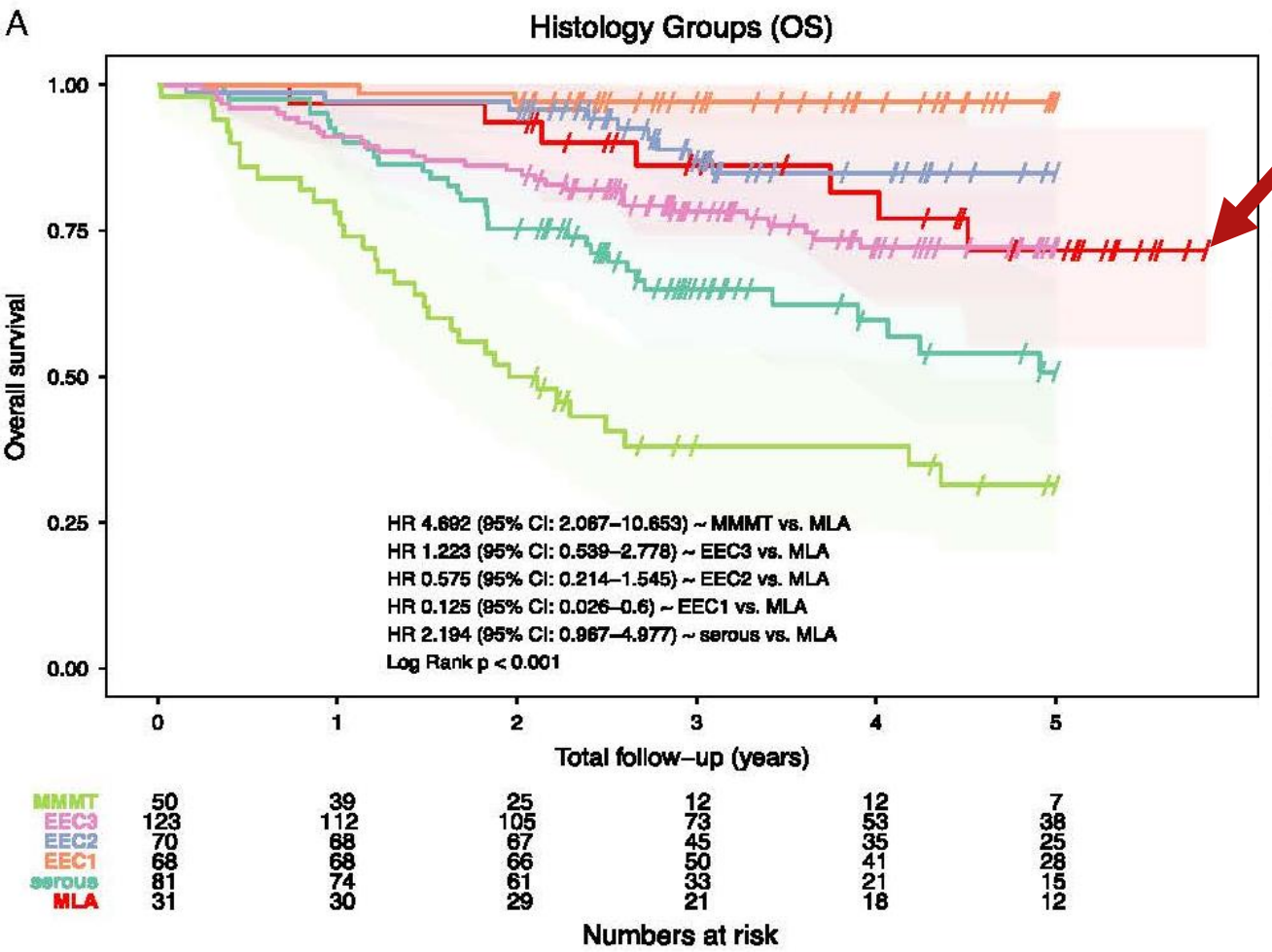
Clinicopathologic Characteristics of Mesonephric Adenocarcinomas and Mesonephric-like Adenocarcinomas in the Gynecologic Tract

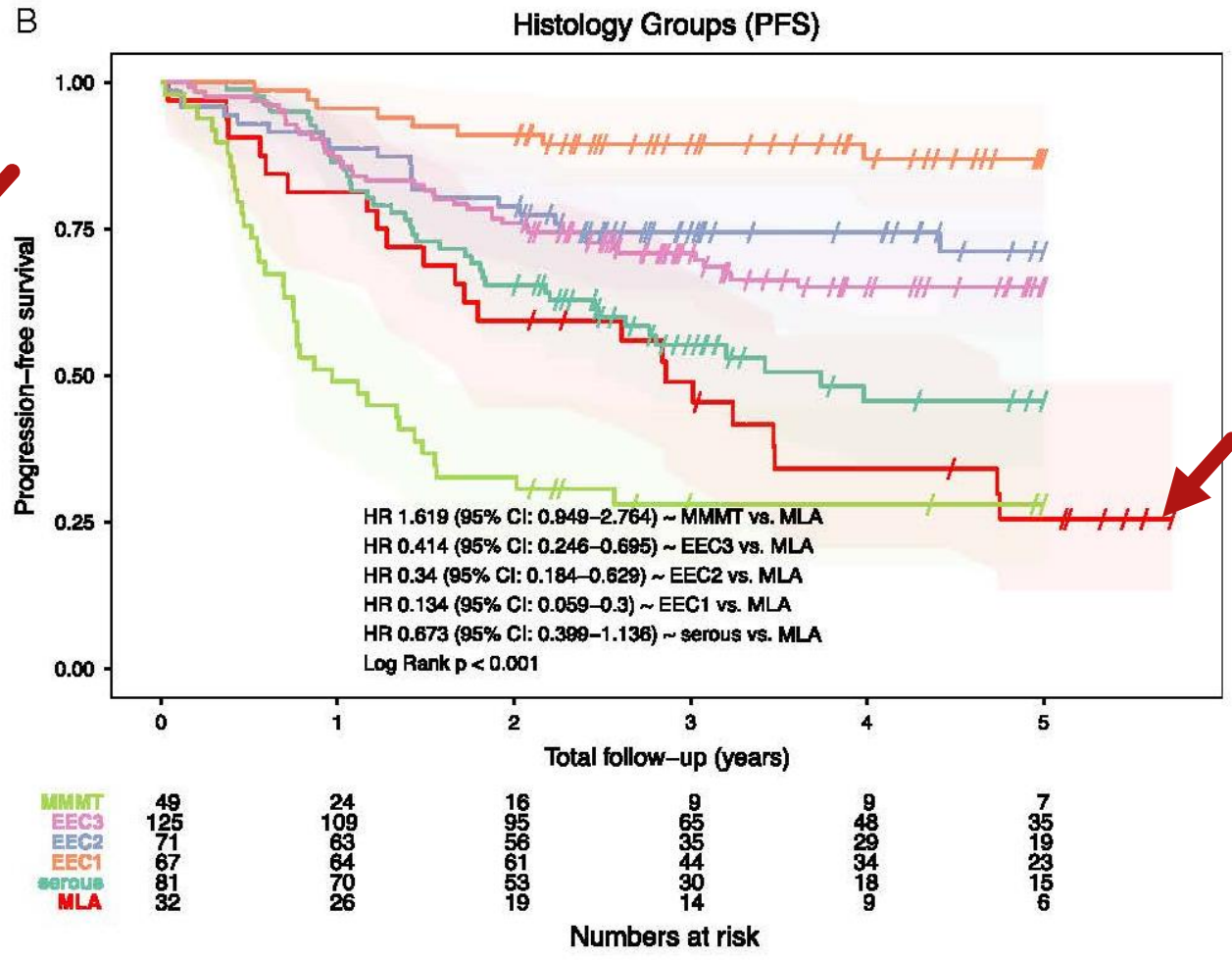
A Multi-institutional Study

Jennifer Pors, MD, Sheila Segura, MD,† Derek S. Chiu, MSc,‡ Noorah Almadani, MD,* Hezhen Ren, MD,* Daniel J. Fix, MD,† Brooke E. Howitt, MD,§ David Kolin, MD,‖ W. Glenn McCluggage, FRCPath,¶ Jelena Mirkovic, MD,# Blake Gilks, MD,*** Kay J. Park, MD,† and Lynn Hoang, MD****

- Multi-institutional study.
- Endometrial (n=44), ovarian (n=25) mesonephric-like carcinomas, and cervical (n=30) mesonephric carcinomas.
- Tumors with ≥2 years follow-up were compared with endometrial Ca from TCGA database.

Pors J. et al. Am J Surg Pathol 2021





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	FIGO Stage II-IV	Recurrence rate	Distant metastasis	5 year disease-specific survival
Mesonephric-like (endometrial)	58%	**59%**	**92%**	72%
Mesonephric-like (ovarian)	39%	42%	56%	71%
Mesonephric (cervical)	60%	50%	**75%**	74%

- Mesonephric neoplasms are clinically aggressive, present at advanced stage, and have predilection for lung metastasis.
- WHO 2020: ‘other carcinomas’.

Pors J. et al. Am J Surg Pathol 2021

Learning Outcome: Endometrial Cancer Reporting beyond 2020 WHO Classification

- Standardize histopathology reporting for endometrial cancers using by ICCR checklist.
- Aware of tumors that are obviously high-grade but have an indolent behavior (POLE*mut*), and others that have a deceptively low-grade histology but are aggressive (NSMP, mesonephric-like).
- Recognize the benefits of adopting a molecular classification for endometrial cancers (for both high-grade and low-grade tumors).
- Acknowledge that there is life beyond the four TCGA molecular subgroups (focus on NSMP).

THANK YOU!

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